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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

WALTER C. **FIERS**
Junior Party
(Application No. 08/471,646),

v.

HARUO **SUGANO**,
MASAMI MURAMATSU, and TADATSUGU TANIGUCHI

Senior Party
(Patent 5,326,859).

Patent Interference No. 105,661

SUGANO OPPOSITION TO FIERS RESPONSE TO ORDER TO SHOW CAUSE

I. INTRODUCTION AND PRECISE RELIEF REQUEST

Pursuant to the Board's authorization, Sugano opposes Fiers Response to Order to Show Cause and moves for termination of this interference in favor of Sugano on the grounds that the subject matter of this interference is not patentably distinct from prior Interference 101,096. In his Response, Fiers argues that under the one-way test, present Count 1 (directed to DNA coding for the mature interferon-β_1[1]) is neither anticipated nor made obvious by the prior Count of Interference 101,096 (directed to DNA coding for interferon-beta) because "[t]here was no distinction between any form of a fibroblast interferon-beta polypeptide, *e.g.,* mature or immature." (Fiers Response[2] at p. 5, ll. 16-21.) However, this argument does not consider the prior Count *as prior art* and *in view of the prior art*. The prior Count as prior art includes the subject matter of the count, which includes the terms of the count as defined by the specification, wherein an interferon-beta DNA is defined by its complete sequence. The prior Count in view of the prior art includes the perspective of the person of ordinary skill, who is presumed to have the knowledge of the relevant prior art at the relevant time period, and therefore the meaning of a fibroblast interferon-beta polypeptide would be informed from this perspective. Accordingly, the person of ordinary skill as of the effective filing date of the involved Fiers application, would have the knowledge of the pre-print manuscript of the Taniguchi *et al.,* Nature (1980) publication because it was widely accessible to the interested public in late March

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[1] Herein, unless otherwise noted, the terms "interferon-β_1", "interferon-beta-1", "interferon-beta", "IFN-beta", "IFN-β", "FIF", and "fibroblast interferon" are used interchangeably.

[2] Herein, Fiers Response to the Order to Show Cause, which is Paper 22, is referred to as the "Fiers Response."

1980. This pre-print discloses the *specific mature interferon sequence* and therefore there was clearly a distinction between the mature and immature forms in the prior art at the time. The person of ordinary skill would also have knowledge of the Knight, Nagata, and Weissenbach publications, which together not only disclose the existence of mature and immature forms, but also the first 13 amino acids of the mature sequence. In view of this prior art, a person of ordinary skill would immediately know the mature interferon sequence given the complete sequence. Further, Sugano presents a copy of a signed, sworn, and notarized affidavit by Dr. Fiers filed in another proceeding, in which he admits that making the mature interferon-beta protein and the DNA coding for the mature protein from the complete sequence required only routine methods to a person of ordinary skill in the art as of March 1980.

This Opposition will show that the one-way test is not satisfied because the prior Count is anticipated by the present Count 1 and the present Count 1 is anticipated or made obvious by the prior Count when properly considered in view of the prior art. Sugano requests the Order to Show Cause not to be vacated and this interference to be terminated in favor of Sugano.

II. ARGUMENT SETTING OUT REASONS WHY RELIEF SHOULD BE GRANTED

A. Applicable Law

1. One-way test and patentable distinctness between counts

A losing party to an interference proceeding is not entitled to pursue claims that are patentably indistinguishable from the lost count in the interference. In re Deckler, 977 F.2d 1449, 1450, 24 USPQ2d 1448, 1448 (Fed. Cir. 1992). To determine whether a losing party in an interference is barred on the merits from pursuing a count in a second interference between the same parties, it is necessary to determine whether the count in the second interference is "patentably distinct" from the

count in the first interference. The comments to 37 C.F.R. § 41 state that the "one-way test" is the proper test for patentable distinctness. "Patentable distinctness is a one-way test. It is sufficient if the subject matter of either count, treated as prior art, would not have anticipated or rendered obvious the subject matter of the other count." 69 Fed. Reg. 49960, 49990-49991 (August 12, 2004). To show that the one-way test is not satisfied, the subject matter of each count must anticipate or render obvious the subject matter of the other count. The subject matter of the count should include at least the language of the count (and the claims which correspond). Moreover, the specification can be relied upon to serve as a dictionary for the terms appearing in the claims (*counts*). Noelle v. Lederman, 355 F.3d 1343, 1352, 69 USPQ2d 1508, 1515-1516 (Fed. Cir. 2004). Further, when comparing whether claims (*counts*) are directed to the same patentable invention, the analysis includes what the prior art would suggest to the person of ordinary skill in the art. Noelle, 355 F.3d at 1351-1352, 69 USPQ2d at 1515-1516 (Fed. Cir. 2004).

2. Printed publication under 35 U.S.C. § 102

Determining whether a reference is a "printed publication" is a legal question based on the facts and circumstances surrounding the reference's disclosure to persons of skill in the art, and is approached on a case-by-case basis. In re Hall, 781 F.2d 897, 899, 228 USPQ 453, 455 (Fed. Cir. 1986); In re Cronyn, 890 F.2d 1158, 1159, 13 USPQ2d 1070, 1071 (Fed. Cir. 1989); In re Klopfenstein, 380 F.3d 1345, 1349, 72 USPQ2d 1117, 1119-1120 (Fed. Cir. 2004). "Dissemination and public accessibility are the keys to the legal determination whether a prior art reference was 'published.'" Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1568, 7 USPQ2d 1057, 1062 (Fed. Cir. 1988), *cert. denied*, 488 U.S. 892, 109 S.Ct. 288 (1988). If accessibility is proved, there is no requirement to show that particular members of the public actually received the

information. *See* In re Klopfenstein, 380 F.3d at 1350, 72 USPQ2d at 1120 (Fed. Cir. 2004) (a reference was neither distributed nor indexed, but the reference was considered a 'printed publication' because it was shown for approximately three days to members of the public having ordinary skill in the art of the invention); Cooper Cameron Corp. v. Kvaener Oilfield Products, Inc., 291 F.3d 1317, 1323-1324, 62 USPQ2d 1846, 1851 (Fed. Cir. 2002) (distributing task reports to three members and six participants of a joint venture was sufficiently accessible under § 102).

3. Party admissions

Pursuant to 37 C.F.R. § 41.152, the Federal Rules of Evidence ("FRE"), except as otherwise provided, apply to patent interference cases. Under FRE 801(d)(2), a party admission is admissible to prove the truth of the statement itself. *See* Goeddel v. Weissmann, 1995 WL 17831418, *19 (Bd. Pat. App. & Interf. 1995) (unpublished) (denying Goeddel's motion to exclude a memorandum that Weissman had offered into evidence as an admission of a party opponent under FRE 801(d)(2)(A)). Furthermore, such admissions by a party opponent are considered to be of particular relevance and probative value. *See* Akro Corp. v. Luker, 45 F.3d 1541, 1546-1547, 33 USPQ2d 1505, 1509 (Fed. Cir. 1995) (treating statements in letters from patentee to accused infringers as admissions under FRE 801); Baker Oil Tools, Inc. v. Geo Vann, Inc., 828 F.2d 1558, 1561-1562, 4 USPQ2d 1210, 1212-1213 (Fed. Cir. 1987) (finding that a party's prior admissions to the PTO regarding lost interference counts were admissible against that party under FRE 801(d)(2)). *See also* Bergstrom v. Sears, Roebuck and Co., 496 F. Supp. 476, 487 207 USPQ 481, 492-493 (D. Minn. 1980) (finding the "visible inconsistency" between the defendant's stance on obviousness in the current infringement suit and prior positions on obviousness before the PTO were of relevance to the issue of obviousness); Donnelly Corp. v. Gentex Corp. 918 F.Supp. 1126, 1135 (W.D. Mich. 1996) (finding

that defendant's affidavits used in prosecution of a European patent application which contradicted defendant's position in the present case in the U.S., were admissible against the defendant under FRE 801(d)(2) and were "highly relevant" as "admissions against interest").

4. Weight and credibility of a declarant

Pursuant to 37 C.F.R. § 41.158, expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight. *See also* Rohm and Haas Co. v. Brotech Corp., 127 F.3d 1089, 1092, 44 USPQ2d 1459, 1462 (Fed. Cir. 1997). The credibility of a Declarant may be called into question where the Declarant has some connection to the party for whom he is testifying or otherwise has a personal interest in the outcome of the case. The opinion testimony of a party having a direct interest in a pending suit is less persuasive than opinion testimony from a disinterested party. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 294, 227 USPQ 657, 665 (Fed. Cir. 1985).

B. The Counts Are Not Patentably Distinct: The One-Way Test Is Not Satisfied

The one-way test is not satisfied because the '096 Count is anticipated by the present Count, and the present Count is anticipated or made obvious by the '096 Count. Fiers argues that the '096 Count as prior art provides "no distinction between any form of a fibroblast interferon-beta polypeptide, e.g., mature or immature" and that "there was nothing in the Prior Count to suggest that those specific forms of fibroblast interferon-beta even existed." (Fiers Response at p. 5, ll. 16-21.) However, when one considers the '096 Count as prior art, this consideration takes into account not only the language of the count as defined by the specification, but also the perspective of one of ordinary skill in the art as of the relevant time period. Noelle, 335 F.3d at 1351-1353, 69 USPQ2d at 1515-1516.

When considering the Sugano priority application as a dictionary for the '096 Count term "fibroblast interferon," the meaning of this term includes the complete interferon sequence because the specification defines the human fibroblast interferon protein to be coded from this sequence. (SMF ¶¶ 96-99.) In view of the prior art, the person of ordinary skill would understand that "a human fibroblast interferon-beta polypeptide" recited in the '096 Count includes both the mature and immature forms. First, because the Taniguchi pre-print is prior art (SMF ¶¶ 67-70, 73-76), the person of ordinary skill is presumed to have the knowledge of this pre-print, which contains an explicit demarcation of the presequence and mature sequence for interferon-beta (SMF ¶¶ 70, 84-86). Second, the Weissenbach and Nagata prior art publications teach the existence of mature and immature interferon forms, and accordingly would motivate the person of ordinary skill to look for them. (SMF ¶¶ 77-81.) Third, the Knight publication directs those skilled in the art to the first 13 amino acids of the mature interferon. (SMF ¶¶ 47-51, 54, 93-95.) Fourth, in the opinions of Dr. Fiers, Dr. Derynck, and Dr. Roberts, the person of ordinary skill in view of the Knight publication would immediately know the mature sequence within the complete sequence. (SMF ¶¶ 43-54; SMF ¶¶ 93-95.) Fifth, as admitted to by Dr. Fiers and as supported by Dr. Houghton and Dr. Derynck, the making of the mature interferon required only routine methods at the time, and required "no new technology." (SMF ¶¶ 56-65.)

1. The pre-print manuscript of Taniguchi et al., Nature, 285 (1980) is prior art as of the effective filing date of the involved Fiers application

In an Affidavit from another proceeding, Dr. Fiers presented evidence that a pre-print manuscript of the Taniguchi *et al.,* Nature, 285, pp. 547-549 (1980) paper (hereafter referred to as "the Taniguchi pre-print"; Ex. 1006) was widely disseminated by Dr. Weissmann, a co-author of this

paper, to the interested public in late March 1980. (SMF ¶¶ 68-70.) In fact, it was Mr. Haley who informed Dr. Fiers of the details behind the dissemination:

> I have been informed by Mr. Haley and believe that it was Professor Charles Weissmann's practice in 1980 to send pre-prints of interferon-related scientific articles that he authored or co-authored to a large number of addressees shortly after the manuscripts were submitted to a journal for publication. I understand from Mr. Haley that Dr. Weissmann included among his addressees all those whom he understood were working on or interested in interferon research in 1979-1980. Further, I understand from Mr. Haley that Dr. Weissmann put no confidentiality restrictions on the addressees.

(SMF ¶ 68.) The "large number of addressees" refers to the "Mailing List for 'Interferon Manuscripts'" (hereafter referred to as "the Mailing List"), which includes the names of over 100 scientists. (SMF ¶ 69.)

Further, Dr. Weissmann *declared* that he distributed copies of the Taniguchi pre-print (as well as a copy of a "Mantei et al." preprint directed to leukocyte interferon) to the addressees listed on the "Mailing List" in "late March." (SMF ¶¶ 73-75.) Considering that Dr. Weissmann sent out the preprints from Zürich in late March, there should be a strong presumption that the members in the Mailing List located in Switzerland received the pre-prints before the effective filing date of the involved Fiers application, which is April 3, 1980. (SMF ¶¶ 70-75.) Members of the Mailing List located in Switzerland included "Aebi, Bern," "Biogen, Geneva," "Birnstiel, Zurich," "Davies, Geneva," "Hofman, Zurich," "Hohn, Basel," "Lindenmann, Zurich," "Luscher, Bern," "Mach, Geneva," "Spahr, Geneva," "Staehelin, Basel," "Tissieres, Geneva," "Tonegawa, Basel," and "Weber, R., Bern". (*See* Ex. 1004; SMF ¶ 76.)

"Dissemination and public accessibility are the keys to the legal determination whether a prior art reference was 'published.'" Constant., 848 F.2d at 1568, 7 USPQ2d at 1062. If accessibility is

proved, there is no requirement to show that particular members of the public actually received the information. Certainly, the level of public accessibility for the Taniguchi pre-print is greater than that for the reference in In re Klopfenstein, which was neither distributed nor indexed but shown for approximately three days to members of the public, or for the report in Cooper Cameron Corp. v. Kvaener Oilfield Products, Inc., which was distributed to three members and six participants of a joint venture. Accordingly, the Taniguchi pre-print should be considered to be prior art as a printed publication under 35 U.S.C. § 102(a) as of the effective filing date of the involved Fiers application.

2. Dr. Fiers admitted that making the mature interferon is enabled given knowledge of the complete sequence and the prior art

The Fiers Response argues that "[o]ne of skill in the art, armed with the Prior Count, would not have been able to bridge the differences between the fibroblast interferon-beta polypeptide of the Prior Count and the *mature 166 amino acid polypeptide* of Count 1 with a reasonable expectation of success." (Fiers Response, p. 7, ll. 6-9.) Sugano disagrees. The '096 Count properly anticipates or makes obvious the mature interferon because the prior art at the time taught routine methods that enabled one of ordinary skill to make and use the invention. Dr. Fiers himself made this clear.

Dr. Fiers is the sole inventor of U.S. Application No. 08/471,646 and was a member of the Scientific Board of Biogen from 1979 until 1989. (SMF ¶¶ 29-30.) The corresponding Canadian Application, No. 374,378, was in a conflict proceeding in the Canadian Patent Office between Biogen, The Japanese Foundation for Cancer Research, and Genentech. That proceeding involved various claims, including Conflict Claim C2, directed to a nucleotide sequence that encodes the specific 166 amino acid sequence of the mature fibroblast interferon, and Conflict Claim C1, directed to the mature fibroblast interferon protein having the 166 amino acid sequence. (¶¶ 32-33, 35-37.) For the Canadian conflict proceeding, Dr. Fiers provided a signed, sworn, and notarized affidavit

dated November 19, 2001 (hereafter referred to as the "Fiers Affidavit" (Ex. 1001), which includes 43 Exhibits (Ex. 1002 and Ex. 1003)). (SMF ¶¶ 38-40; Ex. 1001 at p. 79.) Because Dr. Fiers is an inventor of Application No. 08/471,646 and was a Biogen Scientific Board member, he is a party-opponent to Senior Party Sugano, and therefore statements by Dr. Fiers are admissible as evidence at least as admissions by a party opponent under FRE 801(d)(2). (SMF ¶¶ 29-31.)

There is a visible inconsistency between the sworn statements made by Dr. Fiers in his Affidavit and the position Party Fiers is taking in this matter. In his Affidavit, Dr. Fiers unequivocally stated that one of ordinary skill in 1980 required only routine methods to make a mature fibroblast interferon protein once one had the complete interferon sequence. For example:

> Once we had identified the complete sequence for beta interferon, **I do not believe that there were any other inventive steps required** to develop and perfect the subject matter of the conflict claims. . . . I believe that with the DNA sequence for beta interferon in hand, a person of ordinary skill in the art on March 25, 1980 would have expected to express biologically active beta interferon in E. coli using nothing but routine skill and experimentation. My view is confirmed by two others working in the art and with the beta interferon DNA at this time.

(Emphasis added; SMF ¶ 56; Ex. 1001 at p. 32, ¶ 55.) In the above quote, Dr. Fiers made clear that as of March 25, 1980, one of ordinary skill would only need to use routine skill and experimentation to make mature fibroblast interferon protein once one had the "complete" DNA sequence. By "complete" sequence, Dr. Fiers means the fibroblast interferon sequence that contains the presequence.[3] As shown in Exhibit 15 to the Fiers Affidavit, Dr. Fiers started with the "complete sequence." (SMF ¶ 46; Ex. 1010.) "Using the overlapping portions of clones pHFIF6 and pHFIF7,

[3] Herein, the interferon beta sequence that include the presequence as well as the sequence for the mature interferon is referred to as the "complete sequence."

my laboratory computer operator, whose name I cannot recall, generated the complete sequence of the DNA for beta interferon. I have attached as Fiers Exhibit 15 a March 25, 1980 computer-generated print-out from my laboratory which depicts that DNA sequence." (SMF ¶ 46) This Exhibit shows the DNA sequence for the presequence as well as the coding sequence for the mature interferon protein. (SMF ¶¶ 47, 52-53.) Fiers compared the complete sequence to the Knight's 1980 Science paper to determine where the coding sequence for the mature protein begins.

> By March 25, 1980, I had also compared the deduced N-terminal amino acid sequence displayed on Fiers Exhibit 15 with the 13 N-terminal amino acid sequence published for native human beta interferon. See, e.g., Knight, Science, 207, pp. 525-26 (1980) (Fiers Exhibit 8). Based on this comparison, I was confident that I had cloned the human beta interferon DNA sequence. I also concluded that the sequence contained a 21 amino acid pre- or signal sequence and a 166 amino acid mature sequence. I indicated the start of the mature sequence by a box around the first amino acid ("Met") (Fiers Exhibit 15, pp. 15-16). Thus, I concluded that my March 25, 1980 nucleotide sequence encoded a polypeptide characterized by the 166 amino acid sequence of beta interferon.

(SMF ¶ 47.) After comparing the complete sequence to Knight, Dr. Fiers "concluded" where the presequence and mature sequence were "contained" in the complete sequence. (SMF ¶¶ 47-54.)

As Dr. Fiers repeatedly stated, once one is aware where the mature sequence begins, only routine methods are required for making vectors comprising a DNA sequence that codes for the mature protein. (SMF ¶¶ 55-64.) For example, Dr. Fiers admits that only routine molecular biology techniques like DNA linearization, digestion, and subcloning were needed.

> On March 25, 1980, I also verily believe that producing mature beta interferon in E. coli from a DNA sequence encoding beta interferon would have required nothing but the routine application of the standard techniques of molecular biology. [. . . .] all that was needed to produce mature beta interferon directly was to cleave the DNA encoding pre-beta interferon, like the DNA sequence constructed by me from pHFIF6 and pHFIF7, at a convenient restriction site upstream of the signal sequence or within the signal sequence and digest the cleaved DNA to an area close to the ATG of

> the mature interferon. . . . The resulting sequence would then be used to express mature beta interferon directly in E. coli. Just such technique was used in my laboratory to produce mature beta interferon directly (see ¶ 51, supra).

(SMF ¶¶ 59-60.) In fact, it only took Dr. Fiers "[a]bout two weeks after constructing a gene with the complete DNA sequence for beta interferon from the overlapping pHFIF6 and pHFIF7" to produce biologically active, unglycosylated beta interferon polypeptide in E. coli." (SMF ¶ 56.) Accordingly Dr. Fiers stated "[o]nce we had identified the complete sequence for beta interferon, I do not believe that there were any other inventive steps required to develop and perfect the subject matter of the conflict claims." (SMF ¶ 56.)

The Fiers Affidavit also provides the opinions of "two others" who declared that making the mature interferon polypeptide only required routine steps. (SMF ¶ 56.) The "two others" are Dr. Michael Houghton and Dr. Rik Derynk who each provided Declarations *against* the corresponding Biogen EP patent application in Europe. (SMF ¶¶ 57-58.) Both Dr. Derynck and Dr. Houghton had first-hand experience in cloning and expressing interferon beta at the relevant time period. In 1980, Dr. Houghton was attempting to clone and express beta interferon, and declared: "Once we had obtained the complete IFN-β cDNA, its expression in *E. coli* was **routine and straightforward**. In fact, expression of biologically-active IFN-β was achieved at our very **first** attempt." (Emphasis added; SMF ¶ 57.) Dr. Derynck, who was a member of Dr. Fiers' laboratory in 1980, expressed the same opinion, "**no new technology was required** to achieve the expression of IFN-β, which we accomplished about two months after obtaining possession of the full length cDNA encoding it." (Emphasis added; SMF ¶ 58.) These two non-interested experts who worked on cloning and expressing interferon-beta in 1980 not only believed that making mature interferon protein in bacteria

required only routine methods for the ordinary artisan, but also accomplished this objective quickly and with no new technology.

As shown above, the arguments made by Dr. Fiers in his Affidavit clearly contradict the positions argued in the Fiers Response. Party Fiers should be barred from relying upon such contradictory theories. *See* Bosies v. Benedict, 27 F.3d 539, 544, 30 USPQ2d 1862, 1866 (Fed. Cir. 1994) (a party to an interference cannot rely on one theory to argue that compounds are patentably distinct and then urge another contradictory theory to establish conception); *and* Bigham v. Godtfredsen, 857 F.2d 1415, 1417, 8 USPQ2d 1266, 1268-1269 (Fed. Cir. 1988) (a party to an interference cannot rely on one argument for the purpose of bifurcating a count and subsequently urge a contrary argument for the purpose of proving priority).

3. The one-way test is not satisfied

The subject matter of either count, treated as prior art and in view of the prior art, anticipates or renders obvious the subject matter of the other count. Accordingly, the present Count 1 and the prior Count from Interference No. 101,096 (hereafter referred to as "the '096 Count") are not patentably distinct as the one-way test is not satisfied.

a. The present Count 1 anticipates the '096 Count

If the subject matter of present Count 1 is considered prior art, it would anticipate the '096 Count, because the subject matter of the '096 Count encompasses the complete sequence of interferon-beta with the presequence as well as the sequence of interferon-beta coding only for the mature protein. Fiers cannot disagree with this analysis because in Interference No. 101,096, Fiers argued "a human fibroblast β1 interferon" is "actually a family of products" encompassing the *mature* form. (SMF ¶¶ 80-83.) Fiers made clear that this "family" includes the *mature* interferon.

> Fiers has demonstrated that several different products have the activity of a human fibroblast β1 interferon. For example, Fiers produced "mature" fibroblast β 1 interferon as the active product of G-pPLa-HFIF-67-12ΔM1 and G-pPLa-HFIF-67-12Δ19 BX-2 ...

(SMF ¶¶ 86-87, see *asterisk "*"* after a "family of products" and at footnote.) "[A] generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960).

b. The '096 Count anticipates present Count 1

The pre-print of the Taniguchi *et al.*, Nature, 285, pp. 547-549 (1980) article is prior art as of the effective filing date of the involved Fiers application. (SMF ¶ 34, 67-76.) Because the pre-print contains the complete sequence including demarcations of the presequence and the mature sequence, one of ordinary skill in the art would have knowledge of the mature and the immature sequence of the fibroblast interferon. (SMF ¶¶ 70, 84-86.) Because it is presumed that the person of ordinary skill in the art knows the relevant art at the time of invention, the '096 Count anticipates each and every limitation of present Count 1.

Alternatively, the '096 Count anticipates present Count 1 in view of the '096 Count as prior art, and from the perspective of a person of ordinary skill at the time, who would know the prior art teachings of the Knight, Weissenbach, and Nagata publications. The '096 Count as prior art includes the subject matter of the count, which would include at least the language of the count, and the specifications can be relied on to serve as a dictionary for the terms. Noelle at 1352-1353. *See also* Fiers Response at p. 3, ll. 18-25. In looking to the specification of Sugano's JP priority application as a dictionary for the term "fibroblast interferon" in the '096 Count, one would understand that the meaning of this term includes the complete interferon sequence because the specification defines the human fibroblast interferon protein to be coded from this sequence:

> It is important that in the sequence there exist without any errors the base sequence [three base pairs] corresponding to the amino acid sequence from the amino-terminal to the 13th amino acid of the human fibroblast interferon reported by Knight, et al. [Science vol. 207, p. 525-526, (1980)]. The fact proves that #319-13 plasmid has the human fibroblast interferon mRNA sequence. Further it is apparent from the data of the primary sequence that the plasmid encompasses the entire coding region of the protein of the above mRNA and probably the coding region of the signal peptide.

(SMF ¶ 96.) As stated in the Final Hearing of the '096 interference, the "subject matter at issue relates **to a DNA** which leads to the production of human fibroblast interferon-beta." (SMF ¶ 97.) The interferon beta "DNA" is defined by its sequence, otherwise it would be indefinite. (SMF ¶ 98.) As referred to in the Final Hearing, Fiers himself expressed "I could not state with any certainty that my selected sequence coded for a fibroblast interferon polypeptide," because as the Board explained "[o]nly after Fiers had identified clones having the complete sequence coding for fibroblast interferon and demonstrated that such sequence corresponded to the partial amino acid sequence reported for native fibroblast interferon [*i.e., Knight*] was the patent application completed and filed on April 3, 1980." (SMF ¶ 99.) Thus, the subject matter of the '096 Count includes the complete interferon beta sequence, which is considered prior art for one-way test analyses.

The person of ordinary skill would know the disclosures of the Weissenbach publication (1979) and the Nagata publication (March 1980), which teach the existence of mature and immature forms for interferon beta. (SMF ¶¶ 77-79.) This knowledge would motivate the artisan to look for immature and mature forms, and in combination with the Knight publication, the artisan would be able to immediately determine whether and where a mature sequence is located within a complete interferon sequence. (SMF ¶¶ 93-95.) As admitted to by Dr. Fiers, one simply needs to compare the complete sequence and the Knight publication to know the mature sequence. (SMF ¶¶ 43-44, 46-55.) Further, although Dr. Rik Derynck and Dr. Thomas Roberts were experts for *opposing* parties in

Interference Nos. 105,334 and 105,337, they were both in agreement on the opinion that in view of the Knight publication, a person of ordinary skill would immediately envisage the mature sequence within the complete interferon beta sequence. (SMF ¶¶ 93-95.) The one-way test is not satisfied because the '096 Count anticipates Count 1, as the perspective of one of ordinary skill the art includes the knowledge of the relevant prior art at time, such as the Knight, Weissenbach, and Nagata papers.

Lastly, when the genus is prior art to the species, a genus may be so small that when considered in light of the totality of the circumstances, it could anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic formula inherently anticipated a claimed species within the genus because "one skilled [the] art would . . . envisage *each member*" of the genus. In re Petering, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962) (emphasis in original.) By Fiers own argument, the interferon-beta "family" only covers "several different products" including the mature form. (SMF ¶¶ 80-83.) Thus, the '096 Count also anticipates the present Count 1 under In re Petering because both the mature and immature species are readily envisaged in view of Knight.

c. The '096 Count makes obvious the present Count 1

The '096 Count also makes obvious the present Count 1 because, as expressed above, the '096 Count as prior art includes the complete sequence and in view of the prior art includes knowledge of the Knight publication. Reflecting the perspective of the skilled worker, both Dr. Taniguchi and Dr. Fiers compared the complete interferon beta sequence with the Knight publication. (SMF ¶¶ 45, 47.) Dr. Fiers admitted that this comparison allowed him to know the boundaries of the presequence and of the mature coding sequence. (SMF ¶ 47.) Even Dr. Derynck and Dr. Roberts,

who were experts for *opposing* parties, agree that the person of ordinary skill would immediately know the composition of the mature sequence within the complete sequence given the start location of the mature interferon beta disclosed by the Knight publication. (SMF ¶¶ 93-95.)

Regarding a reasonable expectation of success, as Dr. Fiers admitted, one of ordinary skill as of March 25, 1980 would only require routine methods to make a mature interferon protein in bacteria once one had the complete sequence. Because the Knight publication told one of ordinary skill exactly where the mature sequence began in the complete sequence, only routine methods were required to make vectors or DNA constructs for protein expression of the mature protein in bacteria:

> [A]ll that was needed to produce mature beta interferon directly was to cleave the DNA encoding pre-beta interferon, like the DNA sequence constructed by me from pHFIF6 and pHFIF7, at a convenient restriction site upstream of the signal sequence or within the signal sequence and digest the cleaved DNA to an area close to the ATG of the mature interferon. . . . The resulting sequence would then be used to express mature beta interferon directly in E. coli. Just such technique was used in my laboratory to produce mature beta interferon directly (see ¶ 51, supra).

(SMF ¶¶ 56, 59-60.) Above, Dr. Fiers shows the simplicity of making a DNA consisting essentially of the sequence coding for the mature protein once one knows the precursor sequence. One only had to linearize a vector containing the complete sequence "at a convenient restriction site upstream of the signal sequence or within the signal sequence" and then "digest the cleaved DNA" with enzymes. (SMF ¶ 60.) Dr. Fiers' words cannot be more clear, "[o]nce we had identified the complete sequence for beta interferon, I do not believe that there were any other inventive steps required to develop and perfect the subject matter of the conflict claims." (SMF ¶ 56; *see also* SMF ¶¶ 46, 57-64.)

Thus, Sugano contends that the '096 Count anticipates and makes obvious the Present Count 1, and as the Present Count 1 species anticipates the '096 Count, the one-way test for patentable distinctness is **not** satisfied. Sugano requests the interference to be terminated on this ground.

C. The Opinion of Dr. Darren Baker Should Be Accorded Little or No Weight

In its response, Party Fiers submits the Declaration of Dr. Baker, who asserts that "in the 1979-1980 time frame and today" a person of ordinary skill in the art would not have understood the '096 Count to "identify or distinguish which forms of human fibroblast interferon polypeptide, if any, it included," or to inform "the skilled worker that mature human fibroblast interferon existed," and that the person of ordinary skill, "in view of the Prior Count, would not have been able to identify the mature 166 amino acid human fibroblast interferon polypeptide as set forth in Count 1 with a reasonable expectation of success." (SMF ¶ 87.) But these opinions do not consider the fact that the Knight publication was available prior art. Dr. Fiers himself immediately compared the complete sequence to the Knight publication to determine the mature sequence. (SMF ¶ 47). Both Dr. Derynk and Dr. Roberts agreed that a person of ordinary skill is able to envision a DNA for the mature human fibroblast interferon because of the Knight publication. (SMF ¶¶ 93-95.)

Dr. Baker does not disclose any sufficient basis to support his opinions. In the section of his Declaration entitled "The Materials Considered," Dr. Baker only states that "[i]n reaching my opinions expressed below" he considered only Count 1 of this interference and the '096 Count. (SMF ¶ 88.) Dr. Baker provides no discussion as to why the ordinary skilled worker in the 1979-1980 time frame would not be able to identify the mature 166 amino acid human fibroblast interferon polypeptide from the complete sequence in view of the Knight publication. Whether the time frame is "1979-1980" or "today," the hypothetical person of ordinary skill is presumed to have knowledge of the relevant prior art.

The relevant prior art as of the effective filing date of the involved Fiers application not only informed the person of ordinary skill that there was a mature and immature form of leukocyte

interferon (SMF ¶¶ 77-78), but also that the in vitro translation of the interferon beta mRNA most likely resulted in expression of a precursor rather than mature form (SMF ¶ 79.) The person of ordinary skill would not only be motivated to consider mature and immature forms of interferon (SMF ¶¶ 77-79), but would immediately know where the native or mature form sequence begins in view of the Knight publication (SMF ¶¶ 93-95), let alone in view of the Taniguchi pre-print. It is difficult to understand how a person of ordinary skill would not have a reasonable expectation of success given the fact that comparing nucleotide and amino acid sequences is a routine and fundamental ability to the person of ordinary skill.

Without citation to any publications or data or other materials, we are left with Dr. Baker's personal experience. Unfortunately, Dr. Baker did not begin his baccalaureate studies at the University College of Swansea until 1983. (SMF ¶ 89.) Presumably, Dr. Baker was in secondary school during 1979-1980. Nevertheless, Dr. Baker opines on the relevant time period, "on the basis of my interaction over the years with many scientists, that the level of ordinary skill was less in the 1979-1980 time frame." (SMF ¶ 90.) But Dr. Baker does not identify who any of these scientists are. Certainly, these scientists *cannot include* Dr. Fiers, Dr. Houghton, Dr. Derynck, or Dr. Roberts, who have contradictory positions to Dr. Baker. Dr. Baker does not provide any underlying rationale as to why the person of ordinary skill in 1980 would not: (1) have knowledge of the relevant prior art including the Nagata, Weissenbach, and Knight publications, (2) be able to compare the complete interferon beta sequence with the Knight publication amino acid sequence to deduce the mature sequence based on the basic skill of knowing the DNA codons for amino acids, and (3) be able to conduct standard molecular biology such as linearizing and digesting DNA, and subcloning.

Accordingly, expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight. *See* 37 C.F.R. § 41.158; Rohm and Haas Co, 127 F.3d at 1092, 44 USPQ2d at 1462. The weight of Dr. Baker's opinions is further weakened by bias because he is presently an Associate Director for Biogen. (SMF ¶ 91.) The opinion testimony of a party having a direct interest in a pending suit is less persuasive than opinion testimony from a disinterested party. Ashland Oil, 776 F.2d at 294, 227 USPQ at 665.

Sugano submits that the unsupported and biased testimony from Dr. Baker is insufficient to show cause why this interference should proceed, let alone being sufficient to overcome the overwhelming weight of the admissions from Dr. Fiers. Accordingly, Party Fiers has failed to present a *prima facie* case as to why the present Count 1 is patentably distinct from the '096 Count.

D. Sugano Did Not Concede That the Counts Are Patentably Distinct

Fiers argued that the subject matter of Count 1 and the '096 Count are patentably distinct, and claimed that "Sugano has conceded that distinctness." (Fiers Response at p. 1, l. 6, and p. 6, ll. 12-16.) Sugano did not concede patentable distinctness between these counts. Such a concession would not make any sense, given that Sugano's U.S. Patent 5,326,859 not only contains a claim identical to Count 1 (*i.e.,* claim 6), but also contains a broader claim that encompasses the mature and immature forms (*i.e.,* claim 1). Rather, during the March 17, 2009 teleconference, Sugano merely agreed, as reflected in the Miscellaneous Order, that Count 1 and the '096 Count had different scopes which are patentable. (SMF ¶ 92.)

E. "As a Matter of Equity"

Fiers argued that "[a]s a matter of equity, Fiers should be permitted to contest priority to the patentably distinct Count 1." (Fiers Response at p. 7, ll. 21-22.) But as a matter of equity, Fiers had

this opportunity in Interference No. 101,096.[4] Regardless, this interference should not proceed because Dr. Fiers has admitted that the mature interferon is "not an invention" over the complete sequence and required only routine methods to a person of ordinary skill as of March 1980. Because Sugano's Japanese patent application discloses the complete interferon sequence and the importance of the Knight publication, Sugano asserts that its March 19, 1980 priority date cannot be challenged by Fiers.

III. CONCLUSION

For all the foregoing reasons, the Order to Show Cause should not be vacated and this interference should be terminated in favor of Sugano.

Respectfully Submitted,

Date: May 6th, 2009

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[4] This Opposition does not present estoppel arguments, because Sugano was ordered to reserve such arguments if the interference proceeds to a motions phase." (Paper 4, ll. 10-14.)

APPENDIX 1: LIST OF EXHIBITS CITED IN THIS PAPER

Ex. 1001 November 19, 2001 Affidavit of Dr. Walter C. Fiers ("Fiers Affidavit")

Ex. 1002 Fiers Affidavit Exhibits 1-20

Ex. 1003 Fiers Affidavit Exhibits 21-43

Ex. 1004 Mailing List of Dr. Weissmann for Interferon Manuscripts (also Exhibit 39 of the Fiers Affidavit)

Ex. 1005 Nagata, S. et al., "Synthesis in E. coli of a polypeptide with human leukocyte interferon activity," Nature, Vol. 284, pp. 316-320, 27 March 1980.

Ex. 1006 Pre-Print Manuscript of Taniguchi *et al.*, Nature, 285, pp. 547-549 (1980) (also Exhibit 40 to Fiers Affidavit)

Ex. 1007 Weissenbach, J. et al., "Identification of the Translation Products of Human Fibroblast Interferon mRNA in Reticulocyte Lysates," Eur. J. Biochem., Vol. 98, pp. 1-8 (1979).

Ex. 1008 Pre-Print Manuscript of Mantei *et al.*, "The nucleotide sequence of a cloned human leukocyte interferon cDNA"

Ex. 1009 Knight, Science, 207, pp. 525-26 (1980) (also Exhibit 8 of the Fiers Affidavit).

Ex. 1010 March 25, 1980 Printout of Fiers "Complete Sequence" (also Exhibit 15 of the Fiers Affidavit)

Ex. 1011 Declaration of Dr. Michael Houghton (also Exhibit 30 of the Fiers Affidavit)

Ex. 1012 Declaration of Dr. Rik Derynck (also Exhibit 31 of the Fiers Affidavit)

Ex. 1013 Motion of Junior Party Walter C. Fiers to Amend the Issue by Substitution of Proposed Count 2 for Count 1 or by Addition of Proposed Count 2 and by Addition of Proposed Counts 3-9 *from* Interference No. 101,096

Ex. 1014 Fiers Draft Patent Application of February 22, 1980 (also Exhibit 10 of the Fiers Affidavit)

Ex. 1015 Declaration of Dr. Charles Weissmann with Attachments from Interference Nos. 105,334 and 105,337

Ex. 1016 May 3, 2007 Declaration of Dr. Rik Derynck from Interference Nos. 105,334 and 105,337

Ex. 1017 February 13, 2007 Declaration of Dr. Thomas Roberts with Attachments from Interference Nos. 105,334 and 105,337

Ex. 1018 Goeddel v. Weissmann, 1995 WL 17831418, *19 (Bd. Pat. App. & Interf. 1995).

Ex. 1019 Certified Translation of Sugano Japan Application No. 33931/80 filed March 19, 1980 entitled "Novel recombinant plasmids having the human fibroblast interferon messenger RNA gene"

Ex. 1020 Final Hearing January 17, 1990 for Patent Interference No. 101,096

Ex. 2003 Declaration of Darren P. Baker, Ph.D.

Ex. 2004 Curriculum vitae of Darren P. Baker, Ph.D.

APPENDIX 2: RESPONSE AND STATEMENT OF MATERIAL FACTS ("SMF")

Sugano Response to Fiers' Statement of Material Facts

1. The Board of Patent Appeals and Interferences ("the Board") declared this interference (105,661) on March 4, 2009 between Fiers U.S. patent application 08/471,646 ("the Fiers application") and Sugano U.S. patent 5,326,859 ("the Sugano patent"). *See* Paper 1, Part E. -- Admitted.

2. There is a single Count in this interference -- it is claim 6 of the Sugano patent. *See* Paper 1, Part F. -- Admitted.

3. In this interference, Fiers was designated junior party and Sugano was designated senior party. *See* Paper 1, Part E. -- Admitted.

4. On March 4, 2009, the Board placed Fiers under an Order to Show Cause ("Order") why judgment on priority should not be entered against him. *See* Paper 3. -- Admitted.

5. The Order stated that the interfering subject matter was the same as the Count in prior Interference 101,096 (the "Prior Count") between Fiers, Sugano, and a third party (Revel). *See* Paper 3, p. 1, lines 6-8; Exhibit 2001, p. 1. -- Denied. Paper 3, p. 1, lines 5-8 recites: "There would appear to be no reason to proceed with the present interference since a determination of priority of the subject matter of the count was made in interference 101,096. Instead, it would appear to be appropriate to enter judgment again[st] Fiers as to the present count."

6. The Order stated that there was no reason to proceed with this interference because judgment on priority was entered against Fiers in that prior interference. *See* Paper 3, p. 2, lines 3-7; Exhibit 2001, pp. 7-9. -- Admitted.

7. The Order stated that adverse judgment on priority should be entered against Fiers in this interference. *See* Paper 3, p. 2, lines 7-8. -- Admitted.

8. Fiers and Sugano had a teleconference with APJ Lane on March 17, 2009. *See* Paper 4, p. 1, lines 4-10. -- Admitted.

9. During the March 17, 2009 teleconference, Fiers argued that the Order was based on a mistake of fact and that the subject matters of this interference and the prior Interference 101,096 were not the same. *See* Paper 4, p. 2, lines 4-7. -- Admitted.

10. During the March 17, 2009 teleconference, Fiers argued that the subject matters of this interference and the prior Interference 101,096 had different scopes and were patentably distinct. -- Admitted.

11. During the March 17, 2009 teleconference, Sugano agreed that subject matters of this interference and the prior Interference 101,096 were of different patentable scope but did not agree that the DNA of Count 1 fell within the scope of the Prior Count. -- Denied. Sugano agreed that the '096 Count and the present Count 1 are of different scope. (*See* Paper 4, p. 2, l. 9.) However, Sugano did **not** state that the '096 Count and the present Count 1 are *patentably distinct*.

12. Claim 6 of the Sugano patent recites the following:
A DNA consisting essentially of a DNA which codes for mature human fibroblast interferon polypeptide having the amino acid sequence:

```
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
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Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
Thr Gly Tyr Leu Arg Asn.

See Paper 1, Part F, lines 4-6. -- Admitted.

13. Count 1 of this interference specifies a DNA which codes for: (1) a specific polypeptide: mature human fibroblast interferon polypeptide and (2) a specific 166 amino acid sequence. Exhibit 2003, ¶ 18. -- Admitted to the extent that the specific 166 amino acid sequence is the amino acid sequence for the mature human fibroblast interferon polypeptide.

14. The single count in Interference 101,096 was Count 2 (the "Prior Count") which recites the following:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

See Exhibit 2001, p. 2. -- Admitted.

15. The Prior Count specified a DNA which codes for a human fibroblast interferon-beta polypeptide. *See* Exhibit 2001, p. 2; Exhibit 2003, ¶¶ 16, 17. Admitted to the extent that this Prior Count encompasses both the DNA that codes for the mature and the DNA that codes for the immature human fibroblast interferon.

16. The Prior Count does not refer to a mature human fibroblast interferon beta. *See* Exhibit 2001, p. 2; Exhibit 2003, ¶ 17. Denied. The Prior Count implicitly or inherently refers to a mature human fibroblast interferon beta because the prior art included the Knight publication, the Nagata publication, the Weissenbach publication, and the Taniguchi pre-print. *See* at least Sugano SMF ¶¶ 45-79 and 93-95 below. Further, in Interference 101,096, Fiers argued that interferon-β1 is a "family" that covers the mature species. *See* Sugano SMF ¶¶ 80-83 below.

17. The Prior Count does not distinguish between any form of a human

fibroblast interferon-beta polypeptide, *e.g.*, mature or immature. *See* Exhibit 2001, p. 2; Exhibit 2003, ¶ 17. Denied. The Prior Count implicitly or inherently refers to a mature human fibroblast interferon beta because the prior art included the Knight publication, the Nagata publication, the Weissenbach publication, and the Taniguchi pre-print. *See* at least Sugano SMF ¶¶ 45-79 and 93-95 below. Further, in Interference 101,096, Fiers argued that interferon-β1 is a "family" that covers the mature species. *See* Sugano SMF ¶¶ 80-83 below.

18. The Prior Count does not suggest that specific forms, e.g., mature and immature, of human fibroblast interferon-beta existed. *See* Exhibit 2001, p. 2; Exhibit 2003, ¶¶ 20, 22. Denied. The Prior Count implicitly or inherently refers to a mature human fibroblast interferon beta because the prior art included the Knight publication, the Nagata publication, the Weissenbach publication, and the Taniguchi pre-print. *See* at least Sugano SMF ¶¶ 45-79 and 93-95 below. Further, in Interference 101,096, Fiers argued that interferon-β1 is a "family" that covers the mature species. *See* Sugano SMF ¶¶ 80-83 below.

19. The Prior Count does not recite an amino acid sequence. *See* Exhibit 2001, p. 2; Exhibit 2003, ¶ 17. -- Admitted to the extent that it does not *explicitly* recite an amino acid sequence. Denied with respect to the fact that when the Prior Count is understood in the context of the relevant prior art, a fibroblast interferon or interferon beta polypeptide would be understood to include the specific 166 amino acid sequence listed in present Count 1 in view of the Taniguchi pre-print or because as admitted by Dr. Fiers, the mature sequence in the complete sequence is readily deduced in view of the Knight publication. *See* at least Sugano SMF ¶¶ 45-79 and 93-95 below.

20. Count 1 of this interference is characterized by mature interferon. *See* Paper 1, Part F, lines 4-6; Exhibit 2003, ¶ 18. -- Admitted.

21. Count 1 of this interference is characterized by a specific 166 amino acid sequence. *See* Paper 1, Part F, lines 4-6; Exhibit 2003, ¶ 18. -- Admitted.

22. One of skill in the art, armed with the Prior Count, would not have been

able to bridge the differences between the fibroblast interferon-beta polypeptide of the Prior Count and the mature 166 amino acid polypeptide of Count 1 with a reasonable expectation of success. Exhibit 2003, ¶¶ 20-22. -- Denied. *See* Admissions by Dr. Fiers -- at least Sugano SMF ¶¶ 47-65 below.

23. Armed with the Prior Count, the skilled worker would have had no reasonable expectation of identifying the mature human fibroblast interferon or the specific amino acid sequence of Count 1. Exhibit 2003, ¶ 21. -- Denied. *See* Admissions by Dr. Fiers -- at least Sugano SMF ¶¶ 47-65 below.

24. The skilled worker would not have known from the Prior Count that the mature human fibroblast interferon existed or what its amino acid sequence might have been or how to identify that interferon or its amino acid sequence without the exercise of inventive skill. Exhibit 2003, ¶ 22. Denied. Because the Prior Count is understood in the context of the relevant prior art, a fibroblast interferon or interferon beta polypeptide would be understood to include the specific 166 amino acid sequence listed in present Count 1 in view of the Taniguchi pre-print -- or because as admitted by Dr. Fiers, the mature sequence in the complete sequence is readily deduced in view of the Knight publication. *See* at least Sugano SMF ¶¶ 45-79 and 93-95 below.

25. The Prior Count does not disclose, either explicitly or inherently, each and every limitation of Count 1. Exhibit 2003, ¶ 19. Denied. The Prior Count implicitly or inherently discloses each and every limitation of Count 1 because the Prior Count includes the prior art as of April 2, 1980. The prior art as of the effective filing date of the involved Fiers application included the Knight publication, the Weissenbach publication, the Nagata publication, and the Taniguchi pre-print. *See* at least Sugano SMF ¶¶ 45-79 and 93-95 below.

Sugano Statement of Material Facts

26. Count 1 of the Interference No. 105,661 (referred to herein as "present Count 1") recites: "A DNA consisting essentially of a DNA which codes for mature human fibroblast interferon polypeptide having the amino acid sequence:

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
Thr Gly Tyr Leu Arg Asn." (*See* Paper 1, p. 4.)

27. The Count of Interference No. 101,096 (referred to herein as "the '096 Count") recites: "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." (Paper 3 at p. 1, l. 8 to p. 2, l. 1.)

28. On 15 April 2009, Sugano moved for authorization to file an opposition to Fiers' response to the Order to Show Cause, which was granted. (Paper 30 at p. 2, ll. 1-6.)

29. Walter C. Fiers is the sole inventor of U.S. Application No. 08/471,646, filed June 6, 1995, which is involved in Interference No. 105,661. (Paper 1, at p.3)

30. Walter C. Fiers was a member of the Scientific Board of Biogen from 1979 until 1989. (Ex. 1001 at p. 1, ¶ 2.)

31. The real party-in-interest in U.S. Application No. 08/471,646 is Biogen Idec MA Inc. (Paper 7 at p. 2.)

32. The corresponding Canadian patent application to U.S. Application No. 08/471,646 was Canadian Application No. 374,378, filed April 1, 1981, entitled "DNA Sequences, Recombinant DNA Molecules and Processes for Producing Human Fibroblast Interferon-Like Polypeptides." (Ex. 1001.)

33. Both U.S. Application No. 08/471,646 and Canadian Application No. 374,378 claim priority to U.K. Application 80.18701 filed June 6, 1980 and U.K. Application 80.11306, filed April 3, 1980. (Paper 9 and Ex. 1001.)

34. The Federal Circuit held that Fiers is entitled only to the benefit of the April 3, 1980 filing date of U.K. Application 80.11306 for priority of the '096 Count. (*See* Paper 3, footnote 1 and Fiers v. Revel, 984 F.2d 1164, 1172 (Fed. Cir. 1993).)

35. In 2002, Fiers Canadian Application No. 374,378 was in a conflict proceeding against Sugano Canadian Application No. 363,628 and Goeddel Canadian Application 386,573. (Ex. 1001.)

36. The Conflict Claims in the Canadian conflict proceeding between Fiers, Sugano, and Revel included fourteen different Conflict Claims, including C1 and C2 copied below:

Conflict Claim C1:

An unglycosylated polypeptide characterized by the amino acid sequence

```
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
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Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
Thr Gly Tyr Leu Arg Asn.

Conflict Claim C2:

A nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
Thr Gly Tyr Leu Arg Asn.

(*See* Fiers Affidavit, Ex. 1001 at p. 56 and p. 45.)

37. The amino acid sequences listed in SMF ¶ 36 immediately above for Conflict Claims C1 and C2 is identical to the amino acid sequence encoded by the DNA that is the subject matter of present Count 1.

38. James Haley, who is lead counsel for Fiers in this interference, also represented Fiers (Biogen) in the Canadian Conflict proceeding involving Fiers Canadian Application No. 374,378.

39. The Affidavit of Walter C. Fiers (herein referred to as "the Fiers Affidavit") including its Exhibits was prepared for the Canadian Conflict proceeding involving Fiers Canadian Application No. 374,378. (Ex. 1001, Ex. 1002, Ex. 1003.)

40. The Fiers Affidavit (Ex. 1001) was signed and sworn-to by Walter C. Fiers on November 19, 2001, before Christof Gheeraert, a notary public at Drongen, which is a submunicipality of the city of Ghent (Gent) in the country of Belgium. (Ex. 1001 at p. 79.)

41. In 1980, James Haley worked with Dr. Fiers to draft a patent application directed to interferon beta. (Ex. 1001 at p. 20, ¶ 33.)

42. James Haley and Dr. Fiers prepared a draft patent application dated February 22, 1980. (*See* Fiers Affidavit, Ex. 1001 at ¶ 23; *See* Draft patent application, Ex. 1014)

43. The Draft patent application of Feb. 22, 1980 (Ex. 1014) recites the 13 amino acid N-terminal sequence of native human beta interferon that was published on Feb. 1, 1980 in the Knight et al., Science, 207, pp. 52506 (1980) publication. (*See* Fiers Affidavit, Ex. 1001, at p. 14, ¶ 23(g); Draft patent application, Ex. 1014 at p. 2; and Knight Science publication, Ex. 1009 at Fig. 3.)

44. In his Affidavit, Dr. Fiers stated: "The draft application also disclosed that one of the objects of my work was to obtain a DNA that coded for a polypeptide whose amino acid sequence and composition were substantially consistent with authentic beta interferon (Fiers Exhibit 10, p. 9), and disclosed that this could be effected by determining the DNA sequences of my selected sequences and correlating them with the amino acid composition and N-terminal amino acid sequence reported for native beta interferon (Fiers Exhibit 10, p. 27)." (*See* Fiers Affidavit, Ex. 1001, at p. 14, ¶ 23(h); Draft patent application, Ex. 1014 at p. 9.)

45. In his Affidavit, Dr. Fiers stated: "On March 20, 1980 . . . I analyzed some of the nucleotide sequences from clones pHFIF 1-13 [. . . .] At the time of my analyses of this information, I had no knowledge of any other group's complete sequence of the DNA for human beta interferon. I was aware that Dr. Taniguchi had reported at a February 25, 1980 seminar in Zurich (which I did not attend) that he had sequenced his putative beta interferon clone and had confirmed that the amino acid sequence deduced from the sequence corresponded to the 13 N-terminal amino acids

of native beta interferon, published by Knight et al. (Fiers Exhibit 8)." (*See* Fiers Affidavit, Ex. 1001, at p. 17-18, ¶ 28.)

46. In his Affidavit, Dr. Fiers stated: "Using the overlapping portions of clones pHFIF6 and pHFIF7, my laboratory computer operator, whose name I cannot recall, generated the complete sequence of the DNA for beta interferon. I have attached as Fiers Exhibit 15 a March 25, 1980 computer-generated print-out from my laboratory which depicts that DNA sequence (see, pp. 15-16). The print-out also depicts the amino acid sequence, deduced (i.e., encoded) in the correct reading frame, by that nucleotide sequence. The print-out also provided a list of available restriction sites and provided their specific locations in the beta interferon DNA sequence (see, pp. 1-14). With these sites and locations, the DNA sequence could readily be manipulated for further cloning and for insertion into vectors in operative association with expression control sequences to produce beta interferon in E. coli hosts transformed with those vectors." (*See* Fiers Affidavit, Ex. 1001, at p. 18, ¶ 29; *see* Ex. 1010 for print-out.)

47. In his Affidavit, Dr. Fiers stated: "By March 25, 1980, I had also compared the deduced N-terminal amino acid sequence displayed on Fiers Exhibit 15 with the 13 N-terminal amino acid sequence published for native human beta interferon. See, e.g., Knight, Science, 207, pp. 525-26 (1980) (Fiers Exhibit 8). Based on this comparison, I was confident that I had cloned the human beta interferon DNA sequence. I also concluded that the sequence contained a 21 amino acid pre- or signal sequence and a 166 amino acid mature sequence. I indicated the start of the mature sequence by a box around the first amino acid ("Met") (Fiers Exhibit 15, pp. 15-16). Thus, I concluded that my March 25, 1980 nucleotide sequence encoded a polypeptide characterized by the 166 amino acid sequence of beta interferon." (*See* Fiers Affidavit, Ex. 1001, at p. 19, ¶ 30; *see* Ex. 1009 for Knight, Science, 207, pp. 525-26 (1980), also referred to herein as "the Knight publication.")

48. The Knight, Science, 207, pp. 525-26 (1980) publication discloses purified human fibroblast interferon protein from human diploid fibroblast cells. (Ex. 1009 at p. 523, rt. col., 2nd ¶.)

49. The Knight, Science, 207, pp. 525-26 (1980) publication discloses that the purified interferon was functionally tested. "Interferon was assayed by a microtechnique (8) with a vesicular stomatitis virus as the challenge virus. Interferon units are given in National Institutes of Health human fibroblast interferon units." (Ex. 1009 at p. 523, rt. col., 2nd ¶.)

50. The Knight, Science, 207, pp. 525-26 (1980) publication discloses that "[u]sing the automated protein microsequencing technique described in (7), we have determined the sequence of the 13 amino acid residues at the amino terminus of the interferon prepared by this method." (Ex. 1009 at p. 523, rt. col., 1st ¶.)

51. The Knight, Science, 207, pp. 525-26 (1980) publication discloses that the 13 amino acid residues at the amino terminus of the human fibroblast interferon is: Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser. (Ex. 1009 at p. 526, Fig. 3.)

52. The March 25, 1980 Printout of the human fibroblast interferon nucleotide sequence obtained by Dr. Fiers lists the encoded amino acids of the presequence and the mature sequence. (Ex. 1010 at p. 9.)

53. The March 25, 1980 Printout of the human fibroblast interferon nucleotide sequence obtained by Dr. Fiers has a box around the "Met", which is the 22nd amino acid listed. (Ex. 1010 at p. 9.)

54. The N-terminal 13 amino acid residues disclosed in the Knight, Science, 207, pp. 525-26 (1980) publication is identical to the 22nd through the 34th amino acids listed at the ninth page of the March 25, 1980 Printout of the human fibroblast interferon nucleotide sequence obtained by Dr. Fiers. (Compare Ex. 1009 at p. 526, Fig. 3 with Ex. 1010 at p. 9.)

55. In his Affidavit, Dr. Fiers stated: "On March 28 and 29, 1980, I attended the Biogen Scientific Board meeting, which was held in Geneva. I reported to the Board my successful determination of the complete nucleotide sequence of a DNA coding for human beta interferon. I am certain that I displayed the sequence to the Board. I also described to the Board that I would

use standard techniques to reconstruct a complete DNA sequence coding for a human beta interferon from clones pHFIF6 and 7 and to produce beta interferon from that sequence in E.coli. My presentation was reported in the official Biogen minutes of the meeting (Fiers Exhibit 17). I also believe that I provided to Mr. Haley, who was at the Board meeting, a copy of my March 25,1980 amino acid and DNA sequences." (*See* Fiers Affidavit, Ex. 1001, at p. 20, ¶ 32.)

56. In his Affidavit, Dr. Fiers stated: "About two weeks after constructing a gene with the complete DNA sequence for beta interferon from the overlapping clones pHFIF6 and pHFIF7, we had produced a biologically active, unglycosylated beta interferon polypeptide in E. coli. It was produced from our second expression vector construction - - vector 67-12. Within about two weeks after that, we had improved the yield of recombinant beta interferon by 20 to 30 times. Once we had identified the complete sequence for beta interferon, I do not believe that there were any other inventive steps required to develop and perfect the subject mater of the conflict claims. In fact, we followed the protocol that I had discussed with Dr. Remaut, Mr. Derynck and the Biogen Board months before. See ¶¶ 8-11, 26, 27 and 32. I believe that with the DNA sequence for beta interferon in hand, a person of ordinary skill in the art on March 25, 1980 would have expected to express biologically active beta interferon in E. coli using nothing but routine skill and experimentation. My view is confirmed by two others working in the art and with the beta interferon DNA at this time." (*See* Fiers Affidavit, Ex. 1001, at p. 32, ¶ 55.)

57. In his Affidavit, Dr. Fiers stated: "I have attached as Fiers Exhibit 30, a copy of a May 23, 1996 Declaration of Dr. Michael Houghton. It was filed by Opponent Schering AG during opposition proceedings against Biogen's European patent 41313, that corresponds to my Canadian patent application in this conflict. As indicated in the Declaration, Dr. Houghton worked for Searle and was involved in the cloning and expression of beta interferon in 1980. He now works for Chiron, who has licensed its recombinant beta interferon to a competitor of Biogen in the marketing and sale of recombinant beta interferon for the treatment of multiple sclerosis. Nevertheless, Dr. Houghton's opinion is consistent with mine. The expression of a DNA sequence encoding beta interferon in 1980 did not require invention:

> Once we had obtained the complete IFN-β cDNA, its expression in E. coli was routine and straightforward. In fact, expression of biologically-active IFN-β was achieved at our very first attempt ....

[end quote]." (*See* Fiers Affidavit, Ex. 1001, at p. 33-34, ¶ 56; *see* Declaration of Dr. Houghton Ex. 1011 at ¶ 9, emphasis in original.)

58. In his Affidavit, Dr. Fiers stated: "I have also attached a Declaration of Dr. Derynck, my former student (Fiers Exhibit 31). It was also filed by Opponent Schering AG in the European opposition. Dr. Derynck is now a Professor at the University of California (San Francisco) and has no interest or involvement in this conflict proceeding, in the prior European opposition or with Biogen. Dr. Derynck had the same opinion as Dr. Houghton and I did. The expression of a DNA sequence encoding beta interferon in 1980 did not require invention:

> [O]ur goal was to achieve a finite level of expression of IFN-β, however low, in order to prove the feasibility of the commercial production of the recombinant protein, as well as to be the first group to publish on the recombinant synthesis of IFN- β. We pursued this goal with the methodology available to us at that time, and no new technology was required to achieve the expression of IFN- β, which we accomplished about two months after obtaining possession of the full length cDNA encoding it.

[end quote]." (*See* Fiers Affidavit, Ex. 1001, at p. 33, ¶ 57; *see* Declaration of Dr. Derynck Ex. 1012 at ¶ 5, Ex. 1012.)

59. In his Affidavit, Dr. Fiers stated: "On March 25, 1980, I also verily believe that producing mature beta interferon in E. coli from a DNA sequence encoding beta interferon would have required nothing but the routine application of the standard techniques of molecular biology. Unlike many eukaryotic proteins, the DNA sequence encoding mature human beta interferon starts with an ATG (coding for methionine, the first N-terminal amino acid of mature human beta interferon). ATG is the translation start signal for protein production. Therefore, no construction was needed to place an artificial or synthetic ATG translation start codon in front of the sequence encoding mature beta interferon. Most other eukaryotic proteins do not start with an ATG, so additional construction steps are required to express those proteins directly in mature form. These steps, were, however well known on March 25, 1980. See, e.g., Goeddel et al., Nature, 281, pp. 544-48 (1979) (Fiers Exhibit 37). I believe, therefore, that the technique of the Goeddel

paper could also have easily and routinely been used to construct a DNA sequence that would produce mature beta interferon directly. The Goeddel paper, in fact, teaches that its semi-synthetic technique is directly applicable to proteins made as inactive precursors, like beta interferon (Fiers Exhibit 37, p. 546):

> The hybrid DNA cloning techniques described as a route to the cloning and expression of HGH coding sequences in E. coli are generally applicable to other polypeptides which are synthesised initially as inactive precursors and later processed, or for which full length cDNA transcripts are unavailable.

[end quote]." (*See* Fiers Affidavit, Ex. 1001, at p. 38, ¶ 64.)

60. In his Affidavit, Dr. Fiers stated: "Nonetheless, if the skilled worker chose not to use the Goeddel technique, all that was needed to produce mature beta interferon directly was to cleave the DNA encoding pre-beta interferon, like the DNA sequence constructed by me from pHFIF6 and pHFIF7, at a convenient restriction site upstream of the signal sequence or within the signal sequence and digest the cleaved DNA to an area close to the ATG of mature interferon. Such restriction sites were described in my March 25, 1980 print-out (Fiers Exhibit 15). The resulting sequence would then be used to express mature beta interferon directly in E.coli. Just such technique was used in my laboratory to produce mature beta interferon directly (see ¶ 51, supra). A modification of this technique was also used in the Harvard University laboratory of Dr. Ptashne by Dr. Taniguchi when they expressed beta interferon from Taniguchi's pre-beta interferon DNA sequence. See Taniguchi et al., Proc. Natl. Acad. Sci. USA, 77, pp. 5230-5233 (1980) (Fiers Exhibit 25)." (*See* Fiers Affidavit, Ex. 1001, at p. 39, ¶ 65.)

61. In his Affidavit, Dr. Fiers stated: "In light of the foregoing, particularly the affidavit of Rik Derynck, the affidavit of Michael Houghton., and the decisions of the Technical Board of the European Patent Office and the German Federal Patent Court, I believe that my date of invention for all of the conflict claims is necessarily the March 25, 1980 date that I had disclosed the complete DNA sequence encoding human beta interferon and identified which of the amino acids in the sequence encoded mature beta interferon to others. This sequence was the last piece of the puzzle needed to produce recombinant beta interferon. It enabled us, and would have enabled any skilled worker, to produce biologically active beta interferon in E.coli." (*See* Fiers Affidavit, Ex. 1001, at p. 39, ¶ 65.)

62. In his Affidavit, Dr. Fiers stated: "With that sequence in hand, however, I believe that the steps to insert it into a vector and to transform an E.coli host with the vector were obvious and routine. See ¶¶155-67." (*See* Fiers Affidavit, Ex. 1001, at p. 45, 1st full ¶.)

63. In his Affidavit, Dr. Fiers stated: "On March 25, 1980, I had the complete sequence of beta interferon (i.e., the nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence of the conflict claim) and there was no invention required to produce a DNA sequence encoding either a polypeptide having only the recited sequence or having at a minimum that sequence. See ¶¶ 28-32 and 55-67." (*See* Fiers Affidavit, Ex. 1001, at p. 46, last ¶.)

64. In his Affidavit, Dr. Fiers stated: "On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. On that date, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-out depicted both the pre- and mature amino acid sequences of beta interferon. On that date, I also knew how to combine two of my positive clones, pHFIF6 and pHFIF7, to produce the sequence depicted in the print-out. We would use the common PstI restriction site. I had already discussed with Mr. Derynck and Dr. Remaut how to do this before March 25, 1980. See ¶¶ 28-31. And we would use vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy to Mr. Haley. See ¶¶ 28-32. The Board and Mr. Haley knew from my previous discussions with them how I would use the sequence to produce vectors containing the beta interferon nucleotide sequences. See ¶¶ 8-11 and 28-32." (*See* Fiers Affidavit, Ex. 1001, at p. 50, last ¶.)

65. In his Affidavit, Dr. Fiers stated: "I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are verily believed to be true." (*See* Fiers Affidavit, Ex. 1001, at p. 79, ¶ 94.)

66. In his Affidavit, Dr. Fiers stated: "In late February 1980, I learned from Mr. Haley that Dr. Taniguchi, who had been a post-doctoral student in the Weissmann laboratory before 1978, had presented a seminar on his beta interferon project in Professor Weissmann's laboratory in Zurich. I understand from Mr. Haley that Dr. Taniguchi stated that he had determined the nucleotide

sequence of a clone, not described in his earlier publication (Fiers Exhibit 38), and had confirmed that the first 13 amino acids deduced from that sequence were identical to those of native beta interferon. See Fiers Exhibit 8. I did not attend this seminar. I understand, however, from Mr. Haley that Dr. Taniguchi did not disclose the complete nucleotide sequence or amino acid sequence of his clone. Nor did I know of that sequence when my computer technician generated the computer print-out of my sequence on March 25, 1980. I cited Dr. Taniguchi's seminar in my April 3, 1980 application (Fiers Exhibit 10, p. 10). See also Fiers Exhibit 19, p. 10 and my Canadian patent application, p. 10." (*See* Fiers Affidavit, Ex. 1001, at p. 41, ¶ 69.)

67. In his Affidavit, Dr. Fiers stated: "I understand that some time after Dr. Taniguchi's Zurich seminar, he and Dr.Weissmann worked together to prepare an article that compared the DNA and amino acid sequences of Dr. Taniguchi's beta interferon clone with the DNA and amino acid sequences of a clone isolated by Dr. Weissmann and shown by him to produce recombinant alpha interferon." (*See* Fiers Affidavit, Ex. 1001, at p. 41, ¶ 70.)

68. In his Affidavit, Dr. Fiers stated: "I have been informed by Mr. Haley and believe that it was Professor Charles Weissmann's practice in 1980 to send pre-prints of interferon related scientific articles that he authored or co-authored to a large number of addressees shortly after the manuscripts were submitted to a journal for publication. I understand from Mr. Haley that Dr. Weissmann included among his addressees all those whom he understood were working on or interested in interferon research in 1979-1980. Further, I understand from Mr. Haley that Dr. Weissmann put no confidentiality restrictions on the addresses." (*See* Fiers Affidavit, Ex. 1001, at p. 41, ¶ 71.)

69. In his Affidavit, Dr. Fiers stated: "I have attached as Fiers Exhibit 39, a copy of what 1 understand from Mr. Haley and verily believe to be the "Mailing List for 'Interferon' Manuscripts" that Dr. Weissmann used in early 1980. The list includes several scientists at Roche in Nutley (New Jersey), including Drs. Pestka, Horecker, and Skalka. I was also-on Dr. Weissmann's list of addressees. I recall that Roche, and particular Dr. Pestka, and Genentech, and particularly Dr. Goeddel, were working closely on alpha and beta interferon cloning and expression projects in 1979-1980 and I believe that any Roche scientist who received a pre-print from Dr. Weissmann would have immediately provided a copy to Dr. Goeddel's group at

Genentech." (*See* Fiers Affidavit, Ex. 1001, at p. 41, ¶ 72; *see* Ex. 1004 for "Mailing List for 'Interferon' Manuscripts.")

70. In his Affidavit, Dr. Fiers stated: "I have attached as Fiers Exhibit 40, what I understand from Mr. Haley is a copy of a pre-print of the Taniguichi [*sic*] et al., *Nature*, 285, pp. 547-549 (1980) article (Fiers Exhibit 41). The pre-print was submitted to *Nature* on March 24, 1980. (See Fiers Exhibit 41, p. 549). Dr. Weissmann is a co-author. Figure 1 of the pre-print describes the DNA and amino acid sequences of human beta interferon and compares those sequences to the corresponding sequences of alpha interferon. That Figure also indicates that human beta interferon is a 166 amino acid mature protein with a 21 amino acid pre- or signal sequence. Finally, the Figure provides the DNA and amino acid sequences of both pre- and mature human beta interferon (Fiers Exhibit 41, page 548; Fig. 1). I understand from Mr. Haley that Dr. Weissmann sent a pre-print of the Taniguchi article (Fiers Exhibit 40) to those on his "mailing list" within days of March 24, 1980." (*See* Fiers Affidavit, Ex. 1001, at pp. 42-43, ¶ 73; *see* Ex. 1006 for Taniguchi pre-print.)

71. Dr. Fiers was a member of the Scientific Board of Biogen from 1979 until 1989. *See* Ex. 1001 at ¶ 2.

72. Dr. Weissmann was a member of the Scientific Board of Biogen from 1978 until 1988. *See* Ex. 1015 at Tab A, p. 3.

73. In his Declaration of February 13, 2007, Dr. Weissmann stated: "At a meeting I had with Dr. Taniguchi in Zurich, Switzerland at the end of February 1980, we decided to prepare a manuscript for publication in which the sequence similarities between leukocyte - which I and co-workers had cloned and sequenced - and fibroblast interferons was discussed. We, along with co-authors, prepared a manuscript entitled 'Human Leukocyte and Fibroblast Interferons are Structurally Related' for submission for publication. Both interferon sequences appear in Figure 1. A copy of the manuscript, which I will refer to as "Taniguchi preprint" is attached hereto as Tab B (EX. 2023)." (Ex. 1015 at ¶ 8.)

74. In his Declaration of February 13, 2007, Dr. Weissmann stated: "In late March 1980, I caused the Taniguchi preprint to be distributed to numerous researchers in the field, along with a

preprint entitled 'The nucleotide sequence of a cloned human leukocyte interferon cDNA,' authored by Ned Mantei, myself and others, ('Mantei preprint') attached hereto as Tab G (Ex. 2047). I distributed these preprint manuscripts without restrictions, and under no confidentiality obligations." (Ex. 1015 at ¶ 9; *see* Ex. 1008 for Mantei preprint.)

75. In his Declaration of February 13, 2007, Dr. Weissmann stated: "I have reviewed the attached copy of the 'Mailing List for 'Interferon' Manuscripts' attached hereto as Tab D (Ex. 2024). I created this list. The choice of persons on the list was based on my knowledge of scientists and others who were working on projects directly or indirectly related to interferons, including the cloning, structure, function, and clinical applications of interferons. I believe this copy to be a true and accurate copy of the list of scientists and others to whom the Mantei preprint and Taniguchi preprint were distributed in late March 1980." (Ex. 1015 at ¶ 10; *see* Ex. 1004 for Mailing List.)

76. The Weissmann "Mailing List for 'Interferon' Manuscripts" includes the following addressees located in Switzerland: "Aebi, Bern," "Biogen, Geneva," "Birnstiel, Zurich," "Davies, Geneva," "Hofman, Zurich," "Hohn, Basel," "Lindenmann, Zurich," "Luscher, Bern," "Mach, Geneva," "Spahr, Geneva," "Staehelin, Basel," "Tissieres, Geneva," "Tonegawa, Basel," and "Weber, R., Bern". (See Ex. 1004.)

77. The Nagata *et al.* paper recites: "Two major classes of acid-stable (type I) IFs have been recognised in man -- leukocyte interferon (Le-IF), released by stimulated leukocytes, and fibroblast interferon (F-IF), produced by stimulated fibroblasts." (Ex. 1005 at p. 316, rt. col., 1st full ¶.)

78. The Nagata *et al.* paper recites: "Also, it is possible that *E. coli* IF consists of the Le-IF sequence preceded by a signal sequence, as nucleotide sequence analysis of the cloned IF cDNA revealed a region coding for 22 amino acids which follows the first AUG and precedes the stretch coding for **mature** IF (M. Schwartzstein, N. Mantei and M.S., unpublished results)." (Emphasis added; Ex. 1005 at p. 319, last 3 lines rt. col. to p. 320, first 3 lines, lt. col.)

79. The Weissenbach *et al.* paper recites: "Carbohydrates with M_r of several thousand are attached to the interferon polypeptide and their removal reduces significantly the size of the

interferon molecule [25]. If it lacks these carbohydrates, the product *in vitro* could, therefore be smaller than mature interferon. On the other hand, since interferon is an export protein [26], **it may be synthesized as a precursor protein with a slightly larger polypeptide size than the mature chain** [27, 28]. The good agreement between the size of the cell-free product *in vitro* and interferon *in vivo* may be then rather fortuitous." (Emphasis added; Ex. 1007 at p. 7, lt. col., 2nd full ¶.)

80. In Interference No. 101,096, James Haley filed a motion to substitute the original count with "Proposed Count 2," which recited, "A DNA sequence which consists essentially of a DNA which codes for a human fibroblast β1 interferon." (Ex. 1013 (hereafter referred to as the "Motion of Junior Party Walter C. Fiers to Amend the Issue by Substitution of Proposed Count 2 for Count 1") at p. 1 and at p. 19.)

81. The Motion of Junior Party Walter C. Fiers to Amend the Issue by Substitution of Proposed Count 2 for Count 1 stated, "[p]roposed count 2 also more correctly defines the DNA sequences of this interference in terms of a family of human fibroblast β_1 interferons." (Ex. 1013 at p. 3, 1st full ¶.)

82. The Motion of Junior Party Walter C. Fiers to Amend the Issue by Substitution of Proposed Count 2 for Count 1 stated, "proposed count 2 acknowledges that the recited human fibroblast β_1 interferon is actually a family of products.*" (Ex. 1013 at p. 6, 2nd ¶.)

83. In explaining the meaning of the asterisk to the argument that a human fibroblast β_1 interferon is actually a family of products, the Motion of Junior Party Walter C. Fiers to Amend the Issue by Substitution of Proposed Count 2 for Count 1 stated "Fiers has demonstrated that several different products have the activity of a human fibroblast β_1 interferon. For example, Fiers produced 'mature' fibroblast β_1 interferon as the active product of G-pLAa-HFIF-67-12ΔM1 and G-pHLa-HFIF-67-12Δ19 BX-2 [page 88, lines 19-22]. Fiers also produced possible fusion products that had IFN- β_1 activity from G-pPLa-HFIF-67-12 Δ19 and pPLc-HFIF-67-8 [page 88, lines 22-31]." (Ex. 1013 at p. 6, footnote "*".)

84. The Taniguchi pre-print at Figure 1 presents a comparison of the nucleotide sequence of human leukocyte interferon I and human fibroblast interferon cDNA. (Ex. 1006 at Figure 1.)

85. In the Taniguchi pre-print, the Figure legend to Figure 1 states that "S1 to S23 indicate the amino acids of the putative signal sequence; 1 to 166 the amino acids of the interferon polypeptides." (Ex. 1006 at "Figure Legends".)

86. In the Taniguchi pre-print, Figure 1 presents a 166 amino acid sequence starting with a "Met" at position "1" and ending at position 166 with an "Asn," which 166 amino acid sequence is identical to the amino acid sequence listed in present Count 1. (Ex. 1006 at Figure 1.)

87. In his Declaration, Dr. Baker has stated: "In believe that, in the 1979-1980 time frame and today, the ordinary skilled worker would have reasonably understood that the Prior Count did not identify or distinguish which forms of human fibroblast interferon polypeptide, if any, it included. The Prior Count would also have, in my opinion, not told the skilled worker that mature human fibroblast existed." *and* "In my opinion, in the 1979-1980 time frame and today, the ordinary skilled worker, in view of the Prior Count, would not have been able to identify the mature 166 amino acid human fibroblast interferon polypeptide as set forth in Count 1 with a reasonable expectation of success." (Ex. 2003 at p. 5, ¶¶ 20 and 21.)

88. In his Declaration under the Section entitled "The Materials Considered," Dr. Baker states that he has considered Count 1 of this interference and the "Prior Count" or the '096 Count. (Ex. 2003 at p. 3, ¶ 13.)

89. The *Curriculum vitae* of Dr. Baker shows that he attended the University College of Swansea in Wales, U.K. between the years of 1983-1986, culminating in a "B.Sc. Microbiology with First Class Honors" in 1986. (Ex. 2004 at p. 1.)

90. In his Declaration, Dr. Baker has stated: "I also believe, on the basis of my interaction over the years with many scientists, that the level of ordinary skill was less in the 1979-1980 time frame." (Ex. 2003 at p. 4, ¶ 14.)

91. The *Curriculum vitae* of Dr. Baker shows that he is presently employed by Biogen as an Associate Director in the Department of Drug Discovery. (Ex. 2004 at p. 1.)

92. During the March 17, 2009 teleconference in this interference, Sugano agreed that Count 1 of this interference and the '096 Count have different scope that are patentable. Paper 4 states "Sugano agrees that the '096 Count and the present Count are of different scope." (Paper 4, p. 2, ll. 9-10.) Sugano did not state, concede, imply, suggest, or agree that the scope or subject matter of Count 1 and the '096 Count are patentably distinct.

93. In his Declaration of May 3, 2007, Dr. Derynck stated: "The specification of the Japan '931 application provides the recombinant molecule #319-13, as well as the DNA sequence encoding the 187-amino acid precursor form of human fibroblast interferon. In view of the 13 amino-terminal amino acids of human fibroblast interferon disclosed by Knight (Exhibit 1037 [*see p. 100 of Declaration for full citation of Knight publication]*), **those of ordinary skill in the art should have been able to envision a DNA encoding mature human fibroblast interferon having a total of 166 amino acids and unaccompanied by the human fibroblast interferon signal peptide** (*e.g.,* a DNA consisting of base pairs 70-567 of the sequence provided at p. 15) (Exhibit 2013, at 15.). Sugano's specification, however, did not do so." (Emphasis added; Ex. 1016 at ¶ 159.)

94. In his Declaration of February 13, 2007, Dr. Roberts stated: "The Japanese Application No. 55-33931 cites Knight, et al. [Science vol. 207, p. 525-526, (1980); Tab OO]. The Knight paper discloses the sequence of the N-terminal 13 amino acids of the secreted or mature form of human fibroblast interferon. **In view of Knight's disclosure of the sequence of the N-terminal 13 amino acids of human fibroblast interferon, a person of ordinary skill in the field of recombinant DNA technology or bacterial protein expression as of March 19, 1980 would have immediately known the coding sequence for the mature human fibroblast interferon amino acid sequence given within the full-length cDNA sequence**." *Dr. Roberts also stated:* "I have reviewed the English translation of Japanese Patent Application No. 55-3393 1/80 filed on March 19, 1980 (Tab NN; hereafter referred to as the " '931 application"). Page 15 of this application lists the complete nucleotide sequence of the human fibroblast interferon cDNA and encoded amino acids. The complete protein sequence of human fibroblast interferon is also listed because the amino acid sequence contains the leader or presequence of interferon as well as the mature protein sequence. **Although the sequence diagram itself does not annotate where the leader sequence ends and where the mature protein sequence begins, any person of skill in**

the art at the time would have immediately understood the location of the N-terminal start point of the mature interferon sequence. This location would have been immediately known to one of skill in the art because the application also refers to the Knight publication which discloses the first 13 amino acid residues that make up the N-terminal sequence of mature human interferon beta (Knight et al., "Human Fibroblast Interferon: Amino Acid Analysis and Amino Terminal Amino Acid Sequence," Science, vol. 207, pp. 525-526 (1980)(Tab OO)). Figure 3 of the Knight article discloses the N-terminal 13 amino acids of the mature functional human fibroblast interferon protein. This would have been easily matched to the sequence shown on page 15 of the Japanese application." (First quote: Emphasis added; Ex. 1017 at p. 21, footnote 1; Second quote: Emphasis added; Ex. 1017 at p. 61, ¶ 105.)

95. In his Declaration of February 13, 2007, Dr. Roberts stated: "Further, it was known in the art at least by Feb. 2, 1980 (Knight, et al., Science, Vol. 207, p. 525-526, (1 980)), that the secreted, functional form of the human fibroblast interferon protein has an N-terminal sequence of sequence Met-Ser-Tyr-Asn-Leu-Leu-Gly-Phe-Leu-Gln-Arg-Ser-Ser. Thus, in light of this N-terminal sequence information, given the human fibroblast cDNA sequence provided by the Taniguchi Gene paper or Taniguchi Preprint, one of ordinary skill in the art would have known the boundary between the presequence and the coding sequence for the mature interferon (i. e., the secreted functional form) and would desire to make a DNA coding for a mature interferon without presequence because this has been shown to be the secreted, native, functional form of human fibroblast interferon." (Ex. 1017 at p. 23, ¶ 46.)

96. Sugano Japan application No. 33931/80 filed March 19, 1980 lists the complete interferon beta mRNA sequence at page 15. This application also recites immediately following this sequence, "It is important that in the sequence there exist without any errors the base sequence [three base pairs] corresponding to the amino acid sequence from the amino-terminal to the 13th amino acid of the human fibroblast interferon reported by Knight, et al. [Science vol. 207, p. 525-526, (1980)]. The fact proves that #319-13 plasmid has the human fibroblast interferon mRNA sequence. Further it is apparent from the data of the primary sequence that the plasmid encompasses the entire coding region of the protein of the above mRNA and probably the coding region of the signal peptide." (Ex. 1019 at p. 15 for complete sequence, and at p. 16, 1st ¶ for quote.)

97. The Final Hearing in Interference No. 101,096 states: "The subject matter at isue relates to a DNA which leads to the production of human fibroblast interferon-beta, a naturally occurring protein useful in the treatment of viral diseases." (Ex. 1020 at p. 2, 2nd ¶.)

98. The Final Hearing in Interference No. 101,096 states: "It is not sufficient to define the gene by its principal biological property, e.g., encoding for fibroblast interferon-beta, 'because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.' Amgen, Inc., supra." (Ex. 1020 at p. 8 last 3 lines to p. 9, 1st 3 lines.)

99. The Final Hearing in Interference No. 101,096 states: "Fiers testified at page 7 that it was his scientific opinion that until he could show that a selected cDNA either actually expressed fibroblast interferon or coded for an amino acid sequence that corresponded to the partial sequence known for native fibroblast interferon, 'I could not state with any certainty that my selected sequence coded for a fibroblast interferon polypeptide.' Only after Fiers had identified clones having the complete sequence coding for fibroblast interferon and demonstrated that such sequence corresponded to the partial amino acid sequence reported for native fibroblast interferon was the patent application completed and filed on April 3, 1980 (FR 15)." (Ex. 1020 at p. 9, 2nd ¶.)

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a complete copy of the above paper:

SUGANO OPPOSITION TO FIERS RESPONSE TO ORDER TO SHOW CAUSE

has been served by electronic mail on this day May 6th, 2009 upon counsel of record for Junior Party Fiers:

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Respectfully,

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B8/B8 CIP

IN THE CANADIAN PATENT OFFICE

Examiner	:	M. Gillen
Applicant	:	Biogen, Inc.
Application No.	:	374,378
Filed	:	April 1, 1981
For	:	DNA SEQUENCES, RECOMBINANT DNA MOLECULES AND PROCESSES FOR PRODUCING HUMAN FIBROBLAST INTERFERON-LIKE POLYPEPTIDES

AFFIDAVIT OF WALTER C. FIERS

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AFFIDAVIT OF WALTER C. FIERS

I, WALTER C. FIERS, being duly sworn, declare the following:

I. INTRODUCTION

1. I am the inventor of the subject matter described and claimed in Canadian patent application 374,378 (hereinafter "my Canadian patent application"). I understand that subject matter is at issue in a conflict proceeding in the Canadian Patent Office.

2. I am the former Director-Head of the Laboratory for Molecular Biology at the Rijksuniversiteit Ghent, Belgium. I held that position from 1967 until 1996. From 1996-1997, I was Director of the Flanders Interuniversity Institute for Biotechnology, Department of Molecular Biology. From 1969-1996, I was also Professor of Molecular Biology at the Faculty of Sciences, University of Ghent. I became Professor Emeritus in 1996. I was a member of the Scientific Board of Biogen from 1979 until 1989.

3. I received my Ph.D. degree in 1963 from the Rijkslandbouwhoge School in Ghent, Belgium. From 1960-1961, I was a Research Fellow in biology at the California Institute of Technology, Pasadena, California. In 1962 and in 1963, I was a Research Associate at the University of Wisconsin, Madison, Wisconsin.

4. I have conducted research and authored or co-authored more than 850 publications in the field of molecular biology. I am the recipient of numerous scientific awards including the Dr. Beijerinck-Gold Medal for Virology, awarded by the Royal Dutch Academy of Sciences (1986), the Rik & Nel Wouters Prize for Cancer Research (1986), the Artois-Baillet Latour Prize (1989) (a major international award, I was the first Belgian to receive it), and the Robert Koch Prize (1991). Based on my contribution to science and medicine in Belgium, I was made a hereditary Baron by His Majesty the King of Belgium (1990). A copy of my CV and list of publications are attached as Fiers Exhibits 1 and 2.

II. I HAD THE COMPLETE DNA AND AMINO ACID SEQUENCES OF BETA INTERFERON NO LATER THAN MARCH 20, 1980 AND DISCLOSED IT TO OTHERS NO LATER THAN MARCH 25, 1980

5. Beginning in early 1978, I began using recombinant DNA techniques to isolate and clone a DNA sequence which would allow the production of human fibroblast interferon-beta polypeptide ("beta interferon") in cells transformed with a recombinant expression vector that had the cloned DNA in operative association with an expression control sequence. I have attached as Fiers Exhibit 3 notes of an April 21, 1978 meeting that I had with one of my graduate students,

Rik Derynck. These notes reflect one of our early discussions about the beta interferon project. Mr. Derynck's Ph.D. thesis project was directed to the cloning of human beta interferon. After receiving his Ph.D degree in 1981, Dr. Derynck left my laboratory to work at Genentech, whom I understand is also one of the parties to this conflict.

6. The beta interferon project was carried out under my supervision at my laboratories in Ghent, Belgium. In this Declaration when I refer to work that "I" did, I intend to include work done under my supervision and control by my students and colleagues. With respect to this work, it was the practice of the members of my laboratory to keep accurate written records of the experiments they carried out, together with the results of those experiments, in their laboratory notebooks. However, there was no formal practice regarding the dating of the experiments recorded in the notebooks. We were an academic laboratory where specific dates of experiments were not necessary for our research. The same holds true for the witnessing and countersigning of notebook pages. We did not do this. Rather, our research was done in teams of several people. All of us knew almost up to the minute what the others were planning, had done, and what the results were. It was, therefore, at the discretion of the individual scientist as to how frequently, if at all, dates were recorded. In relying on these records herein, I will only rely on actually dated pages for the purpose of establishing dates of invention. Undated pages may be referred to, but only in the context of surrounding dated pages.

7 In early 1978, I designed the protocol that I would follow to obtain a DNA or nucleotide sequence that encoded human beta interferon, i.e., a polypeptide characterized by the amino acid sequence recited in the conflict claims,

and to use that DNA sequence to produce the beta interferon polypeptide that it encoded in E. coli. As I explain in ¶ ¶ 17-21, infra, I do not believe that such protocol constitutes conception of any of the conflict claims. In my scientific opinion, conception of each of those claims requires possession of a DNA encoding beta interferon and confirmation by sequencing or expression that the DNA is that of human beta interferon. This view is consistent with my decision not to file a patent application on my beta interferon project until I had a specific DNA sequence and the necessary confirmatory evidence. See ¶ 17, infra.

8. My early 1978 protocol included the following steps. I would isolate poly(A) RNA from human fibroblast cells that I had induced to produce human beta interferon. I would then use that RNA to produce a collection of cDNAs by reverse transcription. After cloning the cDNAs (i.e., inserting each of the many cDNAs produced from the collection of induced RNAs into vectors and transfecting a population of E.coli host cells with the resulting recombinant vectors), I would then screen the resulting cDNA libraries to identify a clone that was related to beta interferon DNA. I would then use that clone to identify clones containing full-length beta interferon DNA. And, I would use that full-length DNA to produce beta interferon in E. coli cells that had been transformed with a recombinant expression vector in which the interferon DNA was in operative association with an expression control sequence. I discussed this plan with several members of my laboratory, including Dr. Erik Remaut, Mr. Patrick Stanssens and Mr. Rik Derynck. I also discussed my plan with two scientific collaborators whom I asked to join me in the project. One was Professor Jean Content of the Institut Pasteur (Brussels). Dr. Content would assist me in translating beta interferon RNA in oocytes for

biological assay. The other was Professor Erik DeClercq of The Catholic University (Leuven). Professor DeClercq would assist me in inducing cells from which we could isolate an RNA preparation containing beta interferon RNA and in carrying out biological assays for human beta interferon.

9. On December 14, 1978, I met with Mr. Dan Adams and Ms. Deborah Masters, President and Vice President of Biogen, S.A., ("Biogen"), respectively, in Ghent. See Fiers Exhibit 4. Biogen was interested in collaborating with me on the beta interferon project and funding my work on it. I told Mr. Adams and Ms. Masters that the beta interferon project was now underway in my laboratory. I also discussed generally with them my procedure for preparing human beta interferon DNA and using that DNA to produce unglycosylated beta interferon in E. coli. Finally, we discussed some of the antiviral and anticancer therapeutic uses to which pharmaceutical compositions containing this recombinant interferon could be put. As a start-up commercial company, Biogen was particularly interested in these pharmaceutical compositions and uses. By late 1978, a large number of clinical applications for beta interferon had been discussed in the literature and small scale, but successful, clinical applications and compositions of native beta interferon isolated from cells, including fibroblast cells, in the treatment of viruses and tumors had been published. See ¶ 23(i) and the references cited therein, infra.

10. In September 1979, I attended Biogen's Scientific Board meeting in Paris, France, to report on the beta interferon project. On September 21, 1979, I described to Biogen's Scientific Board the following steps which had already been carried out in my laboratory:

(a) Poly(A) RNA containing beta interferon mRNA had been isolated from induced human fibroblast cells.

(b) A partial purification of the poly(A) RNA had been effected using formamide-sucrose gradients. This resulted in an approximately 40-fold enrichment in the beta interferon mRNA content of the poly(A) RNA.

(c) The enriched beta interferon mRNA had been used to prepare cDNA by reverse transcription and the resulting cDNA cloned into plasmid vectors using dA-dT tailing to build a library of clones (i.e., recombinant vectors), at least some of which should contain a cDNA sequence coding for human beta interferon.

(d) I had screened approximately 150 clones (in three groups of 50 clones each) using RNA selection hybridization and oocyte translation and antiviral assays and was proceeding to screen the remaining 20,000 clones, using similarly-sized groups.

11. I also discussed with the Biogen Board, the future steps that I planned to undertake in the project.

(a) When one of the groups of 50 clones had assayed as positive in the antiviral assay, I would subdivide that positive group into successively smaller groups (each of 7 or 8 members, and then individually) until I was able to identify at least one individual clone that assayed positively in the oocyte translation assay;

(b) I would then use the cDNA insert of that clone, or a substantial part of it, to rapidly screen by colony hybridization large numbers of clones to select those that hybridized to my first clone;

(c) I would then prepare restriction maps and sequence the cDNA inserts of these positive clones;

(d) I would use the cDNA sequence that I isolated to construct expression vectors in which the cDNA was located in operative association with an expression control sequence and use those vectors to transform E.coli host cells, which on culturing would produce recombinant human beta interferon. I would assay the expressed protein using standard antiviral assays for interferon biological activity. I would also immunologically characterize the interferon and use other available confirmatory tests, e g., cell specificity.

I have attached as Fiers Exhibit 5 a copy of what I understand to be Mr. Bailey's (of Fish & Neave, Biogen's outside patent counsel) notes of my September 21, 1979 presentation to the Biogen Scientific Board. To avoid any misunderstanding, I would like to explain the statement on page 3 of Mr. Bailey's notes. On that page, he has an entry "System has not worked despite apparent functioning of controls." This refers to a hybrid arrested translation assay that I had considered using to screen my library of clones. In the experiments described here, i.e., the ones that were successful in finding positive groups of clones and ultimately a positive individual clone that contained a DNA sequence related to human beta interferon, I used RNA selection hybridization and oocyte translation as my clone screening assay. As indicated in Mr. Bailey's notes, that assay was working successfully in September 1989.

12. After the September meeting, my laboratory continued its library screening work. Much of it was performed by my graduate students, Rik Derynck and Jan Tavernier. I have attached various pages from Mr. Tavernier's

laboratory notebook from this time frame -- October 29-November 23, 1979 (Fiers Exhibit 6). Dr. Tavernier gave me a copy of his original notebook from which these pages were copied. For example, on October 29, 1979, Mr. Tavernier describes some of his work with our first positive group of 50 clones -- Group C (Fiers Exhibit 6, p. 1). In early November 1979, Mr. Tavernier describes working with our second positive group of 50 clones -- Group O. By "positive," I mean that each group had been assayed by RNA selection hybridization and oocyte translation and shown to contain at least one clone that hybridized to an induced fibroblast RNA that produced antiviral activity, i.e., one of the biological activities of beta interferon, when translated in oocytes.

Because Groups C and O had both assayed positively in the RNA hybridization and translation assays, Mr. Tavernier describes dividing the two groups of 50 clones into smaller groups: C_1 - C_6 and O_1 - O_6, each having 7 or 8 clones. This work was done in late October 1979 through mid-November 1979 and is consistent with the protocol outlined in my September presentation to the Biogen Board. See Fiers Exhibit 5.

I have also attached Mr. Derynck's January 10, 1980 summary of our clone screenings and antiviral assays (Fiers Exhibit 7). I no longer had the original or a copy of this summary in my files. This summary was produced by Dr. Derynck in a prior litigation. I am informed by Mr. Haley and verily believe that this is the complete summary produced by Dr. Derynck.

13. As can be seen on page 2 of the summary, Mr. Derynck indicated that Groups C and O were positive in that they hybridized to RNA that produced antiviral activity in the *in vitro* oocyte assays. The other groups were not

positive. The assay results for these positive groups are specifically described in my Canadian patent application, pp. 41-42.

14. Between November 22, 1979 and January 10, 1980, we continued to assay subgroups C_1 - C_6 and O_1 - O_6. For example, on page 3 of Mr. Derynck's January 10, 1980 summary (Fiers Exhibit 7), he describes the results of our screening of the subgroups C_1 - C_6 and O_1 - O_6. Various of the subgroups were positive, the most promising subgroup being subgroup O_1. We also divided the more positive of those subgroups into their individual members and assayed each of those clones. By January 10, 1980, we had assayed the individual members of subgroups C_1, O_1, and O_3. On pages 5 and 6 of Mr. Derynck's summary (Fiers Exhibit 7), he describes the results of our screening of the individual members of the subgroups C_1, O_1 and O_3. The most positive clone was clone $O_{1:8}$. Mr. Derynck's summary indicates his belief that this clone was positive for interferon activity (page 6 (my translation)). "This $O_{1:8}$ is clearly positive for interferon activity." These results are also referred to in my Canadian patent application, pp. 42-44.

15. We concluded from these results that clone $O_{1:8}$ hybridized (i.e., had a high level of sequence identity) to an RNA that produced beta interferon biological activity in our antiviral assay. It, therefore, contained a cDNA sequence that was related, at least in DNA sequence, to beta interferon. However, further analyses were required to demonstrate that the DNA did, in fact, encode beta interferon. These analyses included sequencing and comparison of the deduced amino acid sequence with that of native beta interferon, or expression of the sequence to produce beta interferon in an E. coli host.

16. The 13 N-terminal amino acid sequence of beta interferon became available in late 1979 and was published in the scientific literature on February 1, 1980. See Knight et al., Science, 207, pp. 525-26 (1980) (Fiers Exhibit 8). It was, therefore, available for comparison with my cloned DNA sequence, particularly for confirming the N-terminal amino acid of mature beta interferon.

17. On January 12, 1980, I attended a meeting of Biogen's Scientific Board in Martinique. At the meeting, I made a presentation on my progress in isolating a DNA sequence that encoded human beta interferon. During the meeting, Biogen's outside patent counsel, Mr. Haley, and I also discussed what information we believed would be required before we could file a patent application properly claiming a DNA or nucleotide sequence coding for human beta interferon. We decided that we would not file the application until I actually had one or more specific DNAs in hand and could show that these DNA sequences either coded for an amino acid sequence that corresponded to the partial amino acid sequence then known for native beta interferon (Knight et al., see, e.g., Fiers Exhibit 8) or actually expressed beta interferon activity. As a result of that decision, and my estimate that I expected to have the necessary data in one to two months time, we agreed to keep in close contact.

18. Our opinion was subsequently validated by United States courts. I verily believe that the United States courts, and in particular the Court of Appeals for the Federal Circuit, have decided in all of the cases that have been before them that conception of a DNA sequence requires more than just a plan to clone the sequence or a recognition of its biological activity. The Federal Circuit has reasoned that a DNA sequence is a chemical compound. As such, conception requires that "the inventor be able to define [the compound] so as to distinguish it from other materials,

and to describe how to obtain it." *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed.Cir. 1991). The Federal Circuit went on to explain (Id.):

> Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred., i.e., until after the gene has been isolated.

19. I understand that the Federal Circuit followed this same logic when it decided the appeal in the interference proceeding between my application, the Taniguchi United States application, and the application of a third party (Revel) not involved in this conflict. The subject matter of the interference was United States priority of invention to a DNA sequence coding for beta interferon. *Fiers v. Revel*, 984 F.2d 1164 (Fed.Cir. 1993). In that interference appeal, the Court held (Id. at 1169):

> The difficulty that would arise if we were to hold that a conception occurs when one has only the idea of a compound, defining it by its hoped-for function, is that would-be inventors would file patent applications before they had made their inventions and before they could describe them.
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> * * *
>
> We conclude that the Board correctly decided that conception of the DNA of the count did not occur upon conception of a method for obtaining it. Fiers is entitled only to the benefit of his April 3, 1980 British filing date [which provided the complete DNA and amino acid sequences of beta interferon], since he did not conceive the DNA of the count [A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide] under section 102(g) prior to that date.

20. I am informed by Johanne Gauthier of Ogilvy Renault and do verily believe that despite the differences between American law and the Canadian law applicable at the relevant time, it is likely that Canadian Courts would have reached a similar conclusion, i.e., that the actual DNA or amino acid sequence was required to claim such sequences or any subject matter characterized by them. I also understand that it is the Canadian Patent Office's practice to require the disclosure of the actual DNA or amino acid sequences in applications claiming such sequences.

21. I did not prevail in the United States interference. The Board held that my earliest United States date for a DNA sequence encoding beta interferon was April 3, 1980, the filing date of my first priority application. I have been informed by Johanne Gauthier of Ogilvy Renault and do verily believe that in this conflict I can rely on my work in Belgium, which I was not entitled to do in the United States interference. As described below, I had the complete DNA and amino acid sequences of beta interferon in Belgium no later than March 25, 1980, the date I disclosed that sequence to others.

22. On my return to Ghent after the January 1980 Biogen meeting, we began to analyze and characterize the $O_{1,8}$ recombinant clone (also called IF-8) and to use it to screen our libraries by colony hybridization. This work is reported, for example, in a collection of relevant pages from Mr. Tavernier's notebook (Fiers Exhibit 9). These pages were copied from Mr. Tavernier's original notebook, which he provided to me. For example, on January 14, 1980, Mr. Tavernier described isolating a HinfI restriction fragment from clone $O_{1,8}$ (Fiers Exhibit 9, p. 7). This fragment contained substantially all of the putative beta interferon cDNA in clone $O_{1,8}$. Mr. Tavernier also described experiments carried out to characterize and size that

fragment (Fiers Exhibit 9, p. 7). He also reported nick-translating the fragment to label it for use as a probe in the colony hybridization of my library of clones (Fiers Exhibit 9, p. 9). Finally, Mr. Tavernier described using the labeled probe to screen our libraries and to identify a number of positive clones (Fiers Exhibit 9, pp. 12-17).

23. On February 18, 1980, Mr. Haley came to Ghent and for the next few days he worked with me and my students to draft a patent application directed to my beta interferon project.

By February 22, 1980, Mr. Haley had completed a draft application reflecting the early February 1980 status of my project. Before leaving Ghent, Mr. Haley gave me a copy of the draft, which included several handwritten corrections and inserts. I have attached a copy of this February 22, 1980 draft application as Fiers Exhibit 10. It consisted of 33 numbered pages of specification, together with three Figures. The draft described the following aspects of my beta interferon project, all of which had been carried out in my laboratory prior to February 22, 1980:

(a) Obtaining mRNA from induced human fibroblasts (Fiers Exhibit 10, pp. 13-16).

(b) Preparing double-stranded cDNAs from the fibroblast mRNA (Fiers Exhibit 10, pp. 16-18).

(c) Cloning the double-stranded cDNAs into plasmids (specifically at the PstI restriction site in the beta lactamase gene of pBR322) (Fiers Exhibit 10, pp. 19-25).

(d) Transforming E. coli with the resulting recombinant plasmid vectors (Fiers Exhibit 10, pp. 22-23, 24-25).

(e) The draft application described groups O and C and subgroup O_1 which had been positive in our screening assays (Fiers Exhibit 10, p. 33). Finally, the application described positive clone $O_{1\beta}$ (Fiers Exhibit 10, p. 34). That clone or recombinant DNA molecule contained a cDNA insert that was capable of hybridizing to an mRNA from total RNA from induced fibroblasts, where that RNA was translatable to interferon antiviral activity in oocytes.

(f) As of February 22, 1980, I was actively engaged in carrying out colony hybridization experiments using a fragment of positive clone $O_{1\beta}$ to screen my library for other related clones. Hence, Mr. Haley included a description of such colony hybridization in the draft application (Fiers Exhibit 10, p. 27).

(g) The draft application also recited the 13 amino acid N-terminal sequence of native human beta interferon that had been reported in late 1979 and published on February 1, 1980. See, e.g., Knight et al., Science, 207, pp. 525-26 (1980) (Fiers Exhibit 8) (Fiers Exhibit 10, p. 2)

(h) The draft application also disclosed that one of the objects of my work was to obtain a DNA that coded for a polypeptide whose amino acid sequence and composition were substantially consistent with authentic beta interferon (Fiers Exhibit 10, p. 9), and disclosed that this could be effected by determining the DNA sequences of my selected sequences and correlating them with the amino acid composition and N-terminal amino acid sequence reported for native beta interferon (Fiers Exhibit 10, p. 27).

(i) The draft application also reported the well known therapeutic and clinical applications that had been described for native beta interferon, even though it was only available from culture cells in small amounts (less than 30 U/ml). See, e.g., Fiers Exhibit 10, pp. 4-6 (and references cited therein).

(j) Finally, the draft application specifically disclosed that it was known that unglycosylated interferon (e.g., that produced using glycosylation inhibitors in native cells) retained most of its biological activity (Fiers Exhibit 10, p. 3).

24. After Mr. Haley left Ghent on February 22, 1980, my laboratory continued our colony hybridization screening using the HinfI restriction fragment of clone $O_{1/8}$ (also named pHFIF 1). We identified 12 additional positive clones (pHFIF 2-13). These clones are referred to in my patent Canadian application at pp. 44-47. They are also referred to in Mr. Tavernier's notebook (Fiers Exhibit 9, pp. 18-25).

25. By late February 1980, we had begun to analyze the 13 clones (pHFIF1-13) using restriction digests (i.e., the DNA inserts from each clone were digested with various restriction enzymes and a map of the clone and its sequence relationship to the other clones determined). This work is reported in Mr. Tavernier's notebook (Fiers Exhibit 9, pp. 18-25). I have also attached two of my notes from this time period, dated February 26, 1980 (Fiers Exhibit 11) and March 2, 1980 (Fiers Exhibit 12), respectively. Both refer to the HinfI fragment of clone $O_{1/8}$ and to clones 3 and 7 that had been selected from our libraries using colony hybridization with the Hinf I fragment. These clones are also designated pHFIF 3 and pHFIF 7. My notes refer specifically to "cl 3 and 7" which I understand to be pHFIF 3 and pHFIF 7. My

February 26, 1980 note (Fiers Exhibit 11) also refers to Rik Derynck's work on preparing the clones for sequencing and our restriction digest work. See also my March 2, 1980 note (Fiers Exhibit 12). At this same time, we also began to determine the nucleotide sequences of several of the clones. This work was carried out by Mr. Guido Volckaert in my laboratory. Finally, in late February - early March 1980, we began to investigate whether any of recombinant vectors pHFIF 1-13 that we had selected by colony hybridization could themselves be used to produce biologically active beta interferon polypeptides in E. coli cells transformed with those vectors. Mr. Derynck was carrying out those experiments. See Dr. Derynck's notebook which describes experiments with pHFIF 6 and 7 (Fiers Exhibit 13). I no longer have the original or a copy of Mr. Derynck's notebook in my possession. The attached notebook was produced by Mr. Derynck during a prior litigation. I am informed by Mr. Haley and verily believe that the copy attached is a true and consecutive set of pages, as produced by Mr. Derynck.

26. Because the beta interferon cDNA of those clones had been inserted in the PstI site of the gene for β-lactamase in pBR322, the cDNA or nucleotide sequence of the putative beta interferon was in operative association with an expression control sequence in those vectors. My February 26, 1980 note (Fiers Exhibit 11) refers to such expression experiments. That note and my March 2, 1980 note (Fiers Exhibit 12) also refer to using the inserts of these clones in other expression vectors that we had constructed in 1978-1979 in our laboratory and had often used prior to this time to express polypeptides in E. coli. These expression vectors were referred to as "SRK" vectors. The "S" referred to my student Patrick Stanssens and the "R" to my colleague Dr. Remaut. I do not recall what the "K"

referred to. They had constructed the vectors so that a nucleotide sequence encoding a desired protein could be inserted in them and be positioned in operative association with an expression control sequence (the P_L promoter) in the resulting recombinant vector. The P_L expression control sequence was known to function as a strong, temperature-inducible promoter in E.coli. My notes show that as early as late February 1980, we were planning to use the SRK expression vectors to express the cDNA clones we had identified in the beta interferon project. See Fiers Exhibits 11 and 12.

27. On March 8, 1980, I prepared a note also setting out my plans for sequencing and expressing the clones that we had identified (Fiers Exhibit 14). By that date, we were already analyzing recombinant vector pHFIF 3 for possible production of a beta interferon polypeptide (see Fiers Exhibit 14). The planning note (p. 2) also refers to using the "SRK" expression vectors for the production of proteins using the DNA inserts of the identified clones.

28. On March 20, 1980, while traveling by train from Brussels to Paris for a March 21-22, 1980 meeting entitled: "Transforming Genes II," I analyzed some of the nucleotide sequences from clones pHFIF 1-13 that Mr. Volckaert had provided to me and some of the restriction digests of those clones that Mr. Tavernier had done. I was able to confirm the date of this meeting and thus the date of my analysis of the beta interferon clones, because I gave a talk at the meeting entitled: "Detailed Study of the Initiation of Transcription in the SV40 System" and because I have a list of all of the meetings that I attended. During the train ride, I determined from my analyses that although none of clones pHFIF 1-13 by themselves contained a complete nucleotide sequence for beta interferon, it was possible to reconstruct the

complete nucleotide sequence of the DNA of human beta interferon by using overlapping regions of clones pHFIF 6 and 7. At the time of my analyses of this information, I had no knowledge of any other group's complete sequence of the DNA for human beta interferon. I was aware that Dr. Taniguchi had reported at a February 25, 1980 seminar in Zurich (which I did not attend) that he had sequenced his putative beta interferon clone and had confirmed that the amino acid sequence deduced from that sequence corresponded to the 13 N-terminal amino acids of native beta interferon, published by Knight et al. (Fiers Exhibit 8). Taniguchi, however, did not make his specific sequence available. Nor was I aware of his sequence. Unfortunately, I do not have any written record of my March 20, 1980 recognition of the full length sequence. I have, therefore, on the advice of my Canadian patent agent, Ogilvy Renault, decided to rely on March 25, 1980 as the first date on which my full length sequence was disclosed to others. See ¶¶ 29-32, infra.

29. Using the overlapping portions of clones pHFIF6 and pHFIF7, my laboratory computer operator, whose name I cannot recall, generated the complete sequence of the DNA for beta interferon. I have attached as Fiers Exhibit 15 a March 25, 1980 computer-generated print-out from my laboratory which depicts that DNA sequence (see, pp. 15-16). The print-out also depicts the amino acid sequence, deduced (i.e., encoded) in the correct reading frame, by that nucleotide sequence. The print-out also provided a list of available restriction sites and provided their specific locations in the beta interferon DNA sequence (see, pp. 1-14). With these sites and locations, the DNA sequence could readily be manipulated for further cloning and for insertion into vectors in operative association with expression control sequences to produce beta interferon in E. coli hosts transformed with those vectors.

30. By March 25, 1980, I had also compared the deduced N-terminal amino acid sequence displayed on Fiers Exhibit 15 with the 13 N-terminal amino acid sequence published for native human beta interferon. See, e.g., Knight, Science, 207, pp. 525-26 (1980) (Fiers Exhibit 8). Based on this comparison, I was confident that I had cloned the human beta interferon DNA sequence. I also concluded that the sequence contained a 21 amino acid pre- or signal sequence and a 166 amino acid mature sequence. I indicated the start of the mature sequence by a box around the first amino acid ("Met") (Fiers Exhibit 15, pp. 15-16). Thus, I concluded that my March 25, 1980 nucleotide sequence encoded a polypeptide characterized by the 166 amino acid sequence of beta interferon.

31. I discussed my March 25, 1980 sequence, and the conclusions I took from it, on that very same day with my laboratory colleagues in Ghent, including Mr. Derynck and Dr. Remaut. As this sequence was the culmination of a research project started some two year earlier, I am confident that the sequence, both DNA and amino acid, was actively discussed by all of the members in my laboratory, working on the beta interferon project, as well as my collaborators in Leuven and Brussels, beginning literally as soon as the sequence came off the printer on March 25, 1980 and continuing for several days. I know that Mr. Volckaert had a copy of the March 25, 1980 sequence. In fact, Mr. Volckaert still had a copy of this long-awaited sequence in his files in October 2001. I also told Mr. Haley about the exciting news -- we had the sequence -- when he telephoned me on March 25, 1980 to check on the progress of our work so he could plan whether he would travel to Ghent after the upcoming March 28-29 Biogen Scientific Board meeting to finish the February 22, 1980 draft

patent application (Fiers Exhibit 10). I understand that Mr. Haley noted our telephone discussion in his 1980 diary (Fiers Exhibit 16).

32. On March 28 and 29, 1980, I attended the Biogen Scientific Board meeting, which was held in Geneva. I reported to the Board my successful determination of the complete nucleotide sequence of a DNA coding for human beta interferon. I am certain that I displayed the sequence to the Board. I also described to the Board that I would use standard techniques to reconstruct a complete DNA sequence coding for a human beta interferon from clones pHFIF6 and 7 and to produce beta interferon from that sequence in E.coli. My presentation was reported in the official Biogen minutes of the meeting (Fiers Exhibit 17). I also believe that I provided to Mr. Haley, who was at the Board meeting, a copy of my March 25, 1980 amino acid and DNA sequences.

33. From March 31 to April 2, 1980, Mr. Haley worked with me and my laboratory colleagues in Ghent to draft the second portion of the specification (pages 39-47), the claims, and the final four drawings of a patent application describing and claiming a DNA coding for human beta interferon (see Fiers Exhibit 18). He had completed the first part of the application on February 22, 1980 (Fiers Exhibit 10) These additional pages described the following aspects of work which had been carried out in my laboratory before April 2, 1980:

(a) Screening of my library of clones by colony hybridization to identify clones that hybridized to my originally selected $O_{\beta 8}$ clone. Twelve clones were selected. One of the clones was additionally assayed to ensure that it was able to select an RNA from the total RNA of

induced fibroblast cells, where that RNA produced interferon activity on translation (Fiers Exhibit 18, pp. 40-42).

(b) A physical map of the cDNA inserts of these clones was constructed by digestion with restriction enzymes and the orientation of the inserts in the various clones was determined (Fiers Exhibit 18, p. 18, Figure 5).

(c) A composite nucleotide sequence was obtained for the inserts of the selected clones and its corresponding amino acid sequence was deduced (Fiers Exhibit 18, Figure 4). From the sequence (Figure 4) and the orientation and restriction maps (Figure 5), I concluded that the complete nucleotide sequence could be obtained by joining fragments from two clones (pHFIF6 and 7) at a common PstI site (Fiers Exhibit 18, pp. 43-45; Figure 4, 6-7).

(d) The mature sequence of human beta interferon comprised 498 nucleotides, which coded for 166 amino acids. The first 13 amino acids reported for native beta interferon were identical to those deduced from the composite gene of Figure 4. The beta interferon sequence also had a 21 amino acid pre- or signal sequence (Fiers Exhibit 18, pp. 44-46).

(e) Figure 6 of the application displayed a comparison of the amino acid composition deduced from my composite sequence with that determined from native beta interferon.

(f) Figure 7 displayed a restriction map of the beta interferon DNA sequence that I had constructed and the strategy used in sequencing three of the inserts of the selected clones -- pHFIF3, 6 and 7.

34. I do verily believe that the patent application, as completed by Mr. Haley in Ghent, was filed in the United Kingdom on April 3, 1980 and was assigned serial number 80-11306. Mr. Haley enclosed a copy of the application, as filed, with his April 18, 1980 letter to me (Fiers Exhibit 19).

35. In late March and early April 1980, my laboratory began to construct a full length DNA coding for human beta interferon. For this work, we used the technique that I had described to the Biogen Scientific Board in March 1980 and that I had referred to in my April 1980 patent application (Fiers Exhibit 18, p. 46).

III. I EXPRESSED A BIOLOGICALLY ACTIVE UNGLYCOSYLATED POLYPEPTIDE CHARACTERIZED BY THE AMINO ACID OF HUMAN BETA INTERFERON NO LATER THAN APRIL 26, 1980

36. Dr. Remaut, my colleague in my laboratory in Ghent, combined the cDNA inserts of the pHFIF 6 and 7 clones. To do this he used the common PstI restriction site in both clones. I have attached pages from Dr. Remaut's notebook reporting these constructions (Fiers Exhibit 20). This construction is also referred to in my Canadian patent application, p. 52.

37. Dr. Remaut made several constructs comprising a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence of beta interferon. See Fiers Exhibit ¶ 20, p. 1. In the first, he used an EcoRI - PstI fragment from pHFIF6 and PstI- HaeII fragment from pHFIF 7. For expression, he inserted this fragment into expression vector pSRK2311 (also named pPLa 2311). We had prepared that expression vector in our laboratory in 1979 and had used it for the expression of various genes in E. coli. The vector was designed so that the DNA to be

expressed could be inserted in operative association with the P_L promoter. In the present case, the insertion resulted in the nucleotide sequence for beta interferon being located in operative association with the P_L expression control sequence of the vector. The resulting expression plasmid was designated pPLaHFIF 67-1 (vector "67-1"). It is described in Dr. Remaut's notebook (Fiers Exhibit 20, p. 1) and in my Canadian patent application, pp. 56-57 and Figure 8.

In the second construct, Dr. Remaut used a BglII - PstI fragment from clone pHFIF6 and a PstI - BglII fragment from clone pHFIF7. See Fiers Exhibit 20, pp. 1-2. He inserted the combined fragment into two other expression vectors that were available and had already been used in my laboratory to express proteins in E. coli -- pST28 (also named pPLa 8) and pSTL24 (also named pPLc 24). The resulting expression vectors were named pPLa-HFIF-67-12 (vector "67-12") and pPLc-HFIF67-8 (vector "67-8"). Again, the insertion resulted in the nucleotide sequence encoding beta interferon being located in operative association with the P_L expression control sequence of the vector. These constructions are also referred to in Dr. Remaut's notebook (Fiers Exhibit 20, pp. 2-3), in my Canadian patent application, pp. 58-63 and Figures 9 and 10, and in Dr. Remaut's notebooks (Fiers Exhibit 21, pp 1-2 and Fiers Exhibit 22, pp. 1-2).

38. I know that expression vectors 67-1 and 67-12 were made no later than the week of April 21-25, 1980. I also believe that vector 67-8 and vector pPLa-HFIF-67-12 Δ19 (vector "67-12 Δ19"), a derivative of vector 67-12, were made at about the same time. Vector 67-12 Δ19 is referred to in my Canadian patent application, pp. 60-61 and Figures 9 and 12. See also Dr. Remaut's notebooks (Fiers Exhibit 21 and 22).

39. The reason that I am certain that expression vectors 67-1 and 67-12 were made no later than the week of April 21-25, 1980 is because of my April 26, 1980 note. I have attached a copy of that note as Fiers Exhibit 23. The note has two parts. The top part was written by one of my students, Eric Saman. It says (my translation):

Induction

After studying the results of the tests from Leuven, the following inductions were planned:

(1) pPLa HFIF 67-12. Both in M5219 as well as in NF1.

(2) pPLc HFIF 67-11 with lac operator.

Mr. Saman signed that part of the note "Eric S." It sets out experiments that we planned to do. I do not know the date Mr. Saman wrote this note about our planned experiments. However, it was certainly before April 26, 1980.

The remainder of the note (Fiers Exhibit 23), as well as the April 26, 1980 date, is in my handwriting. It is my notes of a conversation I had on that date with Mr. Derynck about the results we had obtained in conducting the planned experiments referred to in Mr. Saman's handwriting in the April 26, 1980 note (Fiers Exhibit 23). Those results are reported in Mr. Derynck's handwritten report which is attached to Fiers Exhibit 23. In my original files, the two papers -- my note and Mr. Derynck's report -- are clipped together.

40. Vector 67-12 is referred to in Mr. Saman's part of Fiers Exhibit 23, as well as in the part in my handwriting "12." I know that vector 67-1 was made before vector 67-12. Thus, both vectors were made before April 26, 1980, the date of my note (Fiers Exhibit 23).

41. Mr. Derynck's report, attached to the April 26, 1980 note, is entitled "Report of Biological Results." It refers to an assay of the polypeptides produced in E.coli M5219 and E.coli NF1 cells after transfection with vector 67-12. This assay demonstrated that a biologically active, unglycosylated polypeptide characterized by the amino acid sequence of human beta interferon was produced in E. coli hosts using expression vector 67-12. Mr. Derynck reports <0.2 $\log_{10}$ units/ml of interferon antiviral activity was produced in cells grown at 28°C (a temperature at which the P_L promoter that drives expression of the interferon gene in vector 67-12 is turned off) (i.e., the control cells). By contrast, M5219 cells induced at 42°C (a temperature at which the P_L promoter is active) produced "0.7 $\log_{10}$ units/ml." In my handwritten portions of Fiers Exhibit 23, I have written both Mr. Derynck's "0.7 $\log_{10}$ units/ml" result and the "5 Units/ml" to which those $\log_{10}$ units calculate. I have also written on Mr. Derynck's report next to his notation "0.7," my calculation of the yield "5 U/ml". Because the tests referred to in Mr. Derynck's report take almost a week to run and assay, they must have been done during the few days preceding April 26, 1980, i.e., during the week of April 21-25, 1980.

Because the DNA sequence that I had used to produce this beta interferon was the one depicted in my March 25, 1980 print-out (Fiers Exhibit 15), I concluded that the polypeptide that I had produced was characterized by the 166 amino acid sequence of human beta interferon. Because the beta interferon was produced in E. coli, it would have to be unglycosylated. It was well known for many years that bacterial cells do not glycosylate proteins produced in them.

42. The actual experiment underlying our first production of recombinant beta interferon appears in Mr. Derynck's notebook (Fiers Exhibit 24, p. 1

(Experiment 135)). I do not have the original or a copy of this notebook in my possession. It was produced by Mr. Derynck in a prior litigation. I am informed by Mr. Haley and verily believe that Fiers Exhibit 24 is a true and consecutive set of pages, as produced by Mr. Derynck. Mr. Derynck's laboratory notebook entry (Experiment 135) describes the two experiments set forth in Mr. Saman's handwritten portion of Fiers Exhibit 23. They first refer to the assays of vector 67-11 in NF1 and M5219 cells. They then refer to the assays of vector 67-12 in both types of E.coli cells. Both cells that had been transformed with vector 67-12 produced recombinant beta interferon. The M5219 cells produced 0.7 $\log_{10}$ units/ml and the NF1 cells produced between 0.2 and 0.5 $\log_{10}$ units/ml. The uninduced cells (i.e., the control cells) both produced <0.2 $\log_{10}$ units/ml

43. Confirming the pre-April 26, 1980 date of our first expression of beta interferon is also Mr. Derynck's report itself (attached to Fiers Exhibit 23). It indicates that Mr Derynck was planning additional experiments with expression vector 67-12 "next week," a week in which our assays would be delayed by the May 1 holiday in Belgium. In 1980, May 1 was a Thursday. Mr. Derynck's report specifically says (my translation):

> The main thing is that ... [there is] possibly biological activity in extracts from pPLa - HFIF-67-12 (pSRKB67-12) (best candidate for reinitiation). A light (0.2) activity is observable in the NF1 (after induction), somewhat more (0.7) in the M5219 (after induction). The 28° C controls give <0.2. The main thing here is that the activity in E_tSM <1.0. This is indeed the most important The repeat of the experiment with 2 time samples follows next week.
>
> P.S. Normally they are not doing assays next week in Leuven. (May 1) Eric [DeClercq] was abroad on Friday (until Friday evening) [April 25, 1980]. Would it be possible that you contact him at home in order that the assays could nevertheless be done. Thanks.

Hence, Mr. Derynck was planning to assay the next set of experiments during the week of April 28 - May 2. I have also referred to these planned experiments in my handwritten portion of Fiers Exhibit 23. For example, I have written that vector "12" (vector 67-12) will be tested at 42°C at two time points "t_1 and t_2." And, the very next experiment in Mr. Derynck's notebook (Fiers Exhibit 24) (i.e., "Experiment 136") describes the two time point experiments. The results show that vector 67-12 in E.coli M5219 cells did not produce beta interferon (<0.2 $\log_{10}$ units/ml) after the first time point (time point "a"-- two hours after induction at 42°C) but did produce beta interferon (0.2 $\log_{10}$ units/ml) after the second time point (time point "b" -- 4 hours after induction at 42°C). The first positive expression results with vector 67-12 were, thus, obtained no later than the week before (i.e., the week of April 21-25). Given my April 26, 1980 note, I believe that the latest that the first positive results of our expression of recombinant beta interferon could have been available to us was April 26, 1980. However, I believe the tests were likely done and the results available and understood by Mr. Derynck and me a few days earlier. I am confident I also told Dr. Remaut of the results as soon as we received them from Leuven.

44. Expression vector 67-12 was designed so that transcription would start at the beginning of the β-lactamase gene and continue until two stop or amber codons located just upstream of the sequence coding for beta interferon. See the sequence of the 67-12 vector on pp. 59-60 of my Canadian patent application. We had specifically designed that start-stop construction so that transcription would stop at these stop codons and then reinitiate at the start site of the interferon sequence to produce a beta interferon not fused to any portion of β-lactamase. Mr. Derynck's

report, that is attached to my April 26, 1980 note (Fiers Exhibit 23), specifically refers to this reinitiation, as does my Canadian patent application, pp. 59-60.

45. I know that pre-beta interferon, i.e., beta interferon still containing its signal sequence, is not biologically active. See, e.g., Taniguchi et al., Proc. Natl. Acad. Sci. USA, 77, pp. 5230-33 (1980) (Fiers Exhibit 25). ("We have detected no such activity [antiviral activity characteristic of human beta interferon] in extracts of bacteria synthesizing pre-F-IF" (Fiers Exhibit 25, Abstract).) Therefore, because we had shown that the beta interferon produced from vector 67-12 had biological activity, I believe it was mature human beta interferon. Additionally, subsequent experiments, described below, demonstrated that in M5219 cells (the cells used in our expression of beta interferon from vector 67-12) a portion of the beta interferon produced from vector 67-12 Δ19, a derivative of vector 67-12, and from vector 67-8, was both biologically active and had a size consistent with that of mature human beta interferon. See ¶ 48, infra. The beta interferon coding sequence in those two vectors is the same as that in vector 67-12.

46. In early May 1980, Mr. Derynck also used vectors 67-12 Δ19 and 67-8 to produce biologically active, unglycosylated human beta interferon. Those experiments are reported in his notebook (Fiers Exhibit 24, p. 15). While these specific experiments are not dated, the first page of the exhibit reflects an experiment completed no later than April 26, 1980 (as shown by Fiers Exhibit 23 and the Derynck note attached to it (See ¶¶ 39-43, supra) and the last page is dated June 3, 1980. Given these dates and my review of the intervening pages, it is my scientific opinion, based on the time required to complete the various intervening experiments, that the

positive results demonstrating the production of beta interferon from expression vectors 67-12 Δ19 and 67-8 occurred no later than the May 12-16 time frame.

47. As reported in my Canadian patent application (pp. 79-80) and in Table 1 of Derynck et al., *Nature*, 287, pp. 193-197 (1980) (Fiers Exhibit 26), vectors 67-12 Δ19 and 67-8 produced between 20 and 30-fold higher levels of beta interferon than vector 67-12 (i.e., more than 150 U/ml). Vector 67-12 may have produced less beta interferon because the reinitiation event required for beta interferon expression in that vector is somewhat rare.

48. To determine the size of the beta interferon being produced by expression vectors 67-12 Δ19 and 67-8, we analyzed the proteins produced from those vectors using polyacrylamide gels under denaturing conditions. We then analyzed the various size fractions that had beta interferon antiviral activity. As depicted in Fig. 2 of Fiers Exhibit 26, two main areas of activity were seen in the proteins expressed from each of the two vectors. One had a size consistent with a fusion protein containing beta interferon. The other had "a size compatible with mature but unglycosylated" beta interferon (Fiers Exhibit 26, Abstract). These experiments were done by Mr. Dernyck and reported in his notebook (Fiers Exhibit 27). These pages are not dated. They follow after several intervening pages, a page dated June 3, 1980. Because our paper describing these experiments (Fiers Exhibit 26) was submitted on July 8, 1980 (p. 197), Mr. Dernyck's experiments were certainly completed between June 3, 1980 and July 8, 1980.

49. My expression of a biologically active, unglycosylated polypeptide characterized by the amino acid sequence of human beta interferon was described in British patent application 80-18701, filed June 6, 1980. This application

was prepared by Mr. Bailey, who worked with me and my co-workers in Ghent from June 3-5, 1980, and by Mr. Haley, who worked by phone with Mr. Bailey from New York. A copy is attached as Fiers Exhibit 28.

50. The June 6, 1980 application described various characteristics of the beta interferon that I had produced. It had antiviral activity (Fiers Exhibit 28, pp. 71-73). That activity was neutralized by antisera to native beta interferon (Fiers Exhibit 28, pp. 72-73). It also had the same cell specificity in human, feline, monkey and rabbit cells as native beta interferon (Fiers Exhibit 28, p. 76). Finally, the application described my then ongoing work to improve the yield of beta interferon. It discussed using different expression constructs and described that the beta interferon could be produced as part of a fused protein, in a form able to be processed and secreted by the cell, or directly as a mature protein (Fiers Exhibit 28, pp. 77-80).

51. After June 6, 1980, my laboratory continued, as described in the June 6, 1980 patent application, to work on improving the level of expression of biologically active, unglycosylated human beta interferon. Most of the constructs that we made and tested are described on pp. 63-67 of my Canadian patent application. All produced about the same level of biologically active beta interferon as did original beta expression vectors 67-12Δ19 and 67-8, i.e., more than 150 U/ml. The vector that we constructed to express unglycosylated mature beta interferon directly was derived from one of our original April 1980 expression vectors, vector 67-12Δ19. The construction was simple, although, because of my laboratory's (and Biogen's) limited capabilities in DNA synthesis at that time, we were forced to use a time consuming procedure. We linearized vector 67-12Δ19 with HpaI. We then digested the linearized DNA with Bal31. This enzyme chews back linear DNA from its ends. The time of digestion in

large measure determines the extent of digestion. I had already described using Bal digestion in my February 26, 1980 note (Fiers Exhibit 11). After blunt ending the digested DNA, linkers were added and the DNA recircularized. The resulting vector, pPLa-HFIF-67-12Δ19BX-2, produced biologically active, unglycosylated mature human beta interferon directly. The construction of this vector and the results of mature beta production with it are described on pp. 66-67, 81 of my Canadian patent application.

52. On February 12, 1981, I met with Mr. Haley in Ghent to discuss updating the June 6, 1980 British application for foreign filing. We discussed my most recent beta interferon expression constructions.

53. I understand that Mr. Haley filed the updated application in Canada and in many other countries on April 1-3, 1981.

54. On March 27 and 28, 1981, I attended a Biogen Scientific Board meeting, which was held in Geneva. On March 27, 1981, I reported my continuing work on improving expression levels of beta interferon. By this time, I was also beginning work on the production of beta interferon in mammalian cells. Vectors and expression systems for mammalian cells first became available in early 1981. Beta interferon produced in those cells would be glycosylated. My presentation was reported in the minutes of the meeting (Fiers Exhibit 29).

IV. MY DATE OF INVENTION FOR ALL OF THE CONFLICT CLAIMS IS MARCH 25, 1980

55. About two weeks after constructing a gene with the complete DNA sequence for beta interferon from the overlapping clones pHFIF6 and pHFIF7, we had produced a biologically active, unglycosylated beta interferon polypeptide in E coli. It was produced from our second expression vector construction - - vector 67-12. Within about two weeks after that, we had improved the yield of recombinant beta interferon by 20 to 30 times. Once we had identified the complete sequence for beta interferon, I do not believe that there were any other inventive steps required to develop and perfect the subject mater of the conflict claims. In fact, we followed the protocol that I had discussed with Dr. Remaut, Mr. Derynck and the Biogen Board months before. See ¶¶ 8-11, 26, 27 and 32. I believe that with the DNA sequence for beta interferon in hand, a person of ordinary skill in the art on March 25, 1980 would have expected to express biologically active beta interferon in E. coli using nothing but routine skill and experimentation. My view is confirmed by two others working in the art and with the beta interferon DNA at this time.

56. I have attached as Fiers Exhibit 30, a copy of a May 23, 1996 Declaration of Dr. Michael Houghton. It was filed by Opponent Schering AG during opposition proceedings against Biogen's European patent 41313, that corresponds to my Canadian patent application in this conflict. As indicated in the Declaration, Dr. Houghton worked for Searle and was involved in the cloning and expression of beta interferon in 1980. He now works for Chiron, who has licensed its recombinant beta interferon to a competitor of Biogen in the marketing and sale of recombinant beta interferon for the treatment of multiple sclerosis. Nevertheless, Dr. Houghton's

opinion is consistent with mine. The expression of a DNA sequence encoding beta interferon in 1980 did not require invention.

> Once we had obtained the complete IFN-β cDNA, its expression in *E. coli* was routine and straightforward. In fact, expression of biologically-active IFN-β was achieved at our very first attempt ....

57. I have also attached a Declaration of Dr. Derynck, my former student (Fiers Exhibit 31). It was also filed by Opponent Schering AG in the European opposition. Dr. Derynck is now a Professor at the University of California (San Francisco) and has no interest or involvement in this conflict proceeding, in the prior European opposition or with Biogen. Dr. Derynck had the same opinion as Dr. Houghton and I did. The expression of a DNA sequence encoding beta interferon in 1980 did not require invention.

> [O]ur goal was to achieve a finite level of expression of IFN-β, however low, in order to prove the feasibility of the commercial production of the recombinant protein, as well as to be the first group to publish on the recombinant synthesis of IFN-β. We pursued this goal with the methodology available to us at that time, and no new technology was required to achieve the expression of IFN-β, which we accomplished about two months after obtaining possession of the full length cDNA encoding it.

58. I understand that the Technical Board of the European Patent Office has also held that it was not inventive to express beta interferon, assuming the DNA sequence encoding it was available. It held that the expression of beta interferon, with the DNA sequence for beta interferon in hand, was not inventive as of June 6, 1980. See Fiers Exhibit 32, p. 21:

> At the priority date [June 6, 1980], the recombinant expression of genes from higher eucaryots had already been achieved. Recombinant expression vectors had been constructed for the production of proinsulin, human growth hormone and ovalbumin in a fused state from the P_{amp}, P_{trp} and P_{gal} promoters, respectively (documents (10), (12) and (34). In the same manner, the human growth hormone and SV40 t

> antigen coding sequence had been linked to the P_{lac} promoter in such a way that both proteins could be produced in an unfused state (documents (22) and (23)). In the board's judgment, all of these achievements imply that the insertion of the beta-IFN coding sequence downstream of a promoter so that it would be transcribed from its promoter and subsequently translated in an active form must prima facie have been considered quite feasible.
>
> * * *
>
> [T]o the board, the skilled person would consider the knowledge of the properties of beta-IFN as an asset in identifying in the light of the state of the art which problems, if any, such properties may cause and which solutions were available. By doing so, the skilled person would come to the conclusion that the properties of beta-IFN were not such as to bar the way to its expression.

I know of nothing that would make the Technical Board's decision inapplicable to March 25, 1980 when I had the complete DNA sequence for beta interferon and had disclosed it to others. See ¶¶ 28-32, supra.

59. I also understand that the German Federal Patent Court has decided the same thing: with the DNA sequence of beta interferon in hand, expression of that sequence was not patentable on June 6, 1980 (Fiers Exhibit 33, p. 20):

> However, the subject matter of claim 1 according to the main request is not based on an inventive step.
>
> * * *
>
> The expression of the cDNA known from P 15 [Taniguchi et al., Gene 10, 1980, pp. 11-15 [published May 19, 1980]] and inserted into a vector required only suitable expression control sequences (mainly promoters). No inventive activity was required at the priority date [June 6, 1980] for finding such promoters in order to arrive at the teaching of claim 1 of the main request. Due to its complexity and the resulting need to interlink and perform simultaneously various biochemical and microbiological steps in genetically engineered processes the persons skilled in the art are supposed to be a team of bench biochemists, cell biologists, molecular biologists and microbiologists.
>
> * * *

> In this situation a research team addressed herein as person skilled in the art will perform tests with those expression control sequences that were already described and available at the priority date of the contested patent since the problem of expression - at least at that time - could not be solved by following theoretical approaches alone.
>
> * * *
>
> Therefore, the team will carry out the tests with other expression controls sequences for the expression of eukaryotic genes in prokaryotic host organisms which were already known at the filing date of the contested patent and had been repeatedly described.
>
> The pre-described expression systems include both the promoters of the lac and the trp system as is evident from a list of literature references of the eukaryotic genes expressed at the priority date according to Exhibits P 17 or P 14 of Plaintiff which Defendant does not deny in terms of their content.
>
> * * *
>
> Thus, it was obvious to the team of experts dealing with the problem at the priority date to use such promoter systems also for human fibroblast interferon. No prejudice of the scientific community had to be overcome if only because such promoters had already been successfully used for expressing several proteins, i.e., including human proteins.

Again, I know of no reason that would make the German court's decision inapplicable to the situation on March 25, 1980 when I had the complete DNA sequence encoding beta interferon and had disclosed it to others. See ¶¶ 28-32, supra.

60. In reaching their decision, I understand that the Technical Board and the German Federal Patent Court considered the large number of different genes that had been successfully expressed in E. coli as of June 6, 1980. I have attached, as Fiers Exhibit 34, a Table submitted by Schering AG before the German Federal Patent Court. I understand that a similar Table was before the Technical Board. The Table shows that more than 17 genes had been expressed in E. coli as of June 6, 1980. I

agree that this was the case. And, as can be seen by Fiers Exhibit 34, p. 2, most of these successful expressions had occurred before 1980.

61. I understand that the German Federal Patent Court also held that using the P_L promoter to produce beta interferon was inventive. This specific holding, however, is not relevant to the conflict claims, because those claims are not limited to P_L containing vectors. The conflict claims include all vectors and the German court found the use of such other vectors to be unpatentable and not inventive.

62. On March 25, 1980, I believe that the skilled worker would have expected unglycosylated beta interferon to be biologically active. Scientific reports from 1977 and 1978 had already demonstrated that native beta interferon, which is glycosylated, could be produced in unglycosylated form (e.g., using glycosylation inhibitors, like tunicamycin) and still have biological activity. See, e.g., Stewart, The Interferon System, (1979), p. 181 (Fiers Exhibit 35):

> These data suggest that carbohydrate-free [unglycosylated] interferons are equally active as native glycosylated interferons.

My April 3, 1980 patent application, and the February 22, 1980 draft of it, said the same thing. See Fiers Exhibit 19, pp. 3-4, and Fiers Exhibit 10, p. 3.

63. I have been informed by Mr. Haley of Fish & Neave and believe that the United States Patent and Trademark Office has granted to Genentech United States patent 5,460,811 (Fiers Exhibit 36). The claims of this patent recite a composition comprising "a nonglycosylated polypeptide having the amino acid sequence of mature human fibroblast interferon." I understand from Mr. Haley that during prosecution of the Genentech application, which claimed priority to an

application filed on September 25, 1980 and to a continuation-in-part application filed on August 11, 1981 and issued on October 24, 1995. Genentech argued that it was a surprise and therefore patentable that completely unglycosylated beta interferon was biologically active. However, I understand from Mr. Haley that the above 1979 Stewart statement was not considered by the United States Patent and Trademark Office when it assessed Genentech's argument for patentability. Had it been considered, I do not believe that the '811 patent would have issued. The statement confirms that the claimed compositions were old. Unglycosylated interferon had been described to be active well before Genentech's earliest priority date.

I am also informed by Mr. Haley and verily believe that my United States patent application, corresponding to the Canadian one in conflict, was not considered during prosecution of the granted Genentech patent. It should have been. My application was filed earlier than the earliest Genentech priority application and disclosed the production of unglycosylated beta interferon. At the very least, an interference should have been declared.

Finally I believe that Genentech's argument is inconsistent with what was thought at the time and later confirmed to be true -- unglycosylated beta interferon is biologically active. In my beta interferon project, I always expected that the unglycosylated beta interferon that I intended to produce in E. coli would be biologically active. Had I had any other expectation, it would have made no sense for me, or anyone else of skill in the art, to embark on a beta interferon cloning project in 1979-1980. The only hosts that were available at that time for the expression of cloned DNA sequences were bacterial hosts. They did not glycosylate proteins. Therefore, if anyone believed that unglycosylated beta interferon would not be

biologically active, they would not have put in the significant and time consuming effort to clone its DNA sequence. Plainly, a number of groups, including the three in this conflict, were not deterred by the fact that they could only produce unglycosylated beta interferon from cloned beta interferon DNA in E.coli in 1980. See also Fiers Exhibit 30.

64. On March 25, 1980, I also verily believe that producing mature beta interferon in E. coli from a DNA sequence encoding beta interferon would have required nothing but the routine application of the standard techniques of molecular biology. Unlike many eukaryotic proteins, the DNA sequence encoding mature human beta interferon starts with an ATG (coding for methionine, the first N-terminal amino acid of mature human beta interferon). ATG is the translation start signal for protein production. Therefore, no construction was needed to place an artificial or synthetic ATG translation start codon in front of the sequence encoding mature beta interferon. Most other eukaryotic proteins do not start with an ATG, so additional construction steps are required to express those proteins directly in mature form. These steps, were, however well known on March 25, 1980. See, e.g., Goeddel et al., Nature, 281, pp. 544-48 (1979) (Fiers Exhibit 37). I believe, therefore, that the technique of the Goeddel paper could also have easily and routinely been used to construct a DNA sequence that would produce mature beta interferon directly. The Goeddel paper, in fact, teaches that its semi-synthetic technique is directly applicable to proteins made as inactive precursors, like beta interferon (Fiers Exhibit 37, p. 546):

> The hybrid DNA cloning techniques described as a route to the cloning and expression of HGH coding sequences in E. coli are generally applicable to other polypeptides which are synthesised initially as inactive precursors and later processed, or for which full length cDNA transcripts are unavailable.

65. Nonetheless, if the skilled worker chose not to use the Goeddel technique, all that was needed to produce mature beta interferon directly was to cleave the DNA encoding pre-beta interferon, like the DNA sequence constructed by me from pHFIF6 and pHFIF7, at a convenient restriction site upstream of the signal sequence or within the signal sequence and digest the cleaved DNA to an area close to the ATG of mature interferon. Such restriction sites were described in my March 25, 1980 print-out (Fiers Exhibit 15). The resulting sequence would then be used to express mature beta interferon directly in E.coli. Just such technique was used in my laboratory to produce mature beta interferon directly (see ¶ 51, supra). A modification of this technique was also used in the Harvard University laboratory of Dr. Ptashne by Dr. Taniguchi when they expressed beta interferon from Taniguchi's pre-beta interferon DNA sequence. See Taniguchi et al , Proc. Natl. Acad. Sci. USA, 77, pp. 5230-5233 (1980) (Fiers Exhibit 25).

66. In light of the foregoing, particularly the affidavit of Rik Derynck, the affidavit of Michael Houghton, and the decisions of the Technical Board of the European Patent Office and the German Federal Patent Court, I believe that my date of invention for all of the conflict claims is necessarily the March 25, 1980 date that I had disclosed the complete DNA sequence encoding human beta interferon and identified which of the amino acids in the sequence encoded mature beta interferon to others. This sequence was the last piece of the puzzle needed to produce recombinant beta interferon. It enabled us, and would have enabled any skilled worker, to produce biologically active beta interferon in E.coli.

67. In reaching the above conclusion and in representing what was the relevant date of invention with regards to all of the claims in this conflict, the

following excerpt from the decision of the Supreme Court of Canada in the case of Christiani and Nielson v. Rice [1930] S.C.R. 443 was useful to me.

> If the first inventor has formulated either in writing or verbally, a description which affords the means of making that which is invented and has communicated his invention to others, although without disclosure to the public or application for patent, he is the first and true inventor in the eyes of the present Canadian patent law, so as to prevent any other person from securing a Canadian patent for the same invention."

V. THE COMPLETE DNA SEQUENCE THAT CHARACTERIZES HUMAN BETA INTERFERON WAS PUBLICLY AVAILABLE BY MID-APRIL 1980. AFTER THAT DATE NO ONE COULD CLAIM TO BE AN INVENTOR OF THAT SEQUENCE OR ANY OF THE CONFLICT CLAIMS

68. As early as January 1980, I began hearing rumors that Dr. Taniguchi and his group in Japan had cloned a DNA sequence for beta interferon. There was, however, no information available about any beta interferon DNA sequence. Nor did I know on what evidence Dr. Taniguchi may have been relying in his rumored cloning. Before February 22, 1980, I became aware of Taniguchi et al., Proc. Japan. Acad. Ser. B, 55, pp. 464-69 (1979) (Fiers Exhibit 38). That article described Taniguchi's cloning work. It did not contain any sequence or expression data. It relied solely on RNA selection hybridization data. I believed then and still believe that such data are not appropriate proof for the successful cloning of any gene. RNA selection hybridization is subject to too many possible artifacts. As far as I am aware, Dr. Taniguchi, in fact, has never shown that the clone described in his 1979 article encoded beta interferon. I cited the Taniguchi article (Fiers Exhibit 38) and pointed out my criticisms of it in my February 22, 1980 draft application (Fiers

Exhibit 10, p. 8). See also Fiers Exhibit 19, pp 9-10 and my Canadian patent application, pp. 9-10.

69. In late February 1980, I learned from Mr. Haley that Dr. Taniguchi, who had been a post-doctoral student in the Weissmann laboratory before 1978, had presented a seminar on his beta interferon project in Professor Weissmann's laboratory in Zurich. I understand from Mr. Haley that Dr. Taniguchi stated that he had determined the nucleotide sequence of a clone, not described in his earlier publication (Fiers Exhibit 38), and had confirmed that the first 13 amino acids deduced from that sequence were identical to those of native beta interferon. See Fiers Exhibit 8. I did not attend this seminar. I understand, however, from Mr. Haley that Dr. Taniguchi did not disclose the complete nucleotide sequence or amino acid sequence of his clone. Nor did I know of that sequence when my computer technician generated the computer print-out of my sequence on March 25, 1980. I cited Dr. Taniguchi's seminar in my April 3, 1980 application (Fiers Exhibit 10, p. 10). See also Fiers Exhibit 19, p. 10 and my Canadian patent application, p 10.

70. I understand that some time after Dr. Taniguchi's Zurich seminar, he and Dr. Weissmann worked together to prepare an article that compared the DNA and amino acid sequences of Dr. Taniguchi's beta interferon clone with the DNA and amino acid sequences of a clone isolated by Dr. Weissmann and shown by him to produce recombinant alpha interferon.

71. I have been informed by Mr. Haley and believe that it was Professor Charles Weissmann's practice in 1980 to send pre-prints of interferon-related scientific articles that he authored or co-authored to a large number of addressees shortly after the manuscripts were submitted to a journal for publication. I

understand from Mr. Haley that Dr. Weissmann included among his addressees all those whom he understood were working on or interested in interferon research in 1979-1980. Further, I understand from Mr. Haley that Dr. Weissmann put no confidentiality restrictions on the addresses.

72. I have attached as Fiers Exhibit 39, a copy of what I understand from Mr. Haley and verily believe to be the "Mailing List for 'Interferon' Manuscripts" that Dr. Weissmann used in early 1980. The list includes several scientists at Roche in Nutley (New Jersey), including Drs. Pestka, Horecker, and Skalka. I was also on Dr. Weissmann's list of addressees. I recall that Roche, and particular Dr. Pestka, and Genentech, and particularly Dr. Goeddel, were working closely on alpha and beta interferon cloning and expression projects in 1979-1980 and I believe that any Roche scientist who received a pre-print from Dr. Weissmann would have immediately provided a copy to Dr. Goeddel's group at Genentech.

73. I have attached as Fiers Exhibit 40, what I understand from Mr. Haley is a copy of a pre-print of the Taniguichi et al., *Nature*, 285, pp. 547-549 (1980) article (Fiers Exhibit 41). The pre-print was submitted to *Nature* on March 24, 1980. (See Fiers Exhibit 41, p. 549). Dr. Weissmann is a co-author. Figure 1 of the pre-print describes the DNA and amino acid sequences of human beta interferon and compares those sequences to the corresponding sequences of alpha interferon. That Figure also indicates that human beta interferon is a 166 amino acid mature protein with a 21 amino acid pre- or signal sequence. Finally, the Figure provides the DNA and amino acid sequences of both pre- and mature human beta interferon (Fiers Exhibit 41, page 548, Fig. 1). I understand from Mr. Haley that Dr. Weissmann sent a pre-

print of the Taniguchi article (Fiers Exhibit 40) to those on his "mailing list" within days of March 24, 1980.

74. I also understand that on April 10, 1980, Dr. Weissmann received a "thank you" note for the pre-prints, including the Taniguchi paper from a Dr. Harris in Australia. I have attached a copy of Dr. Harris' letter as Fiers Exhibit 42. Thus, I believe Dr. Weissmann's addressees had received the pre-prints, including the Taniguchi pre-print, by at least mid-April 1980. In fact, Dr. Harris' letter has attached to it a marked-up version of the Taniguchi-Weissmann comparison of the alpha and beta interferon sequences from the Taniguchi pre-print. While I was one of the names on the Weissmann list of addressees, I do not specifically recall when I received the Taniguchi pre-print, but I have no doubt that I did receive it. I do know that I had not received the pre-print before April 3, 1980, when my application describing the cloning and sequencing of the DNA for human beta interferon was filed.

75. Dr. Harris' letter to Dr. Weissmann indicates that he intended to provide copies of the pre-prints, including the Taniguchi pre-print, to others working on interferon in Australia. This indicates to me that the addressees of Dr. Weissmann's pre-prints did not believe that the pre-prints were in any way confidential. Thus, I believe that addressees, like those at Roche, would have made the information, particularly the Taniguchi/Weissmann comparison of the DNA and amino acid sequences of alpha and beta interferon, available to others, i.e., Dr. Goeddel's group, working with them on interferon.

76. As the result of Dr. Weissmann's dissemination of his pre-prints, I believe that by mid-April 1980, the DNA and amino acid sequences that characterize beta interferon were widely available to those interested in interferon and

doing research on it. Accordingly, after that mid-April 1980 date no one could claim as his/her invention the cloning or sequencing of beta interferon. Nor could anyone claim, after that mid-April 1980 date, any invention in the use of that DNA sequence to produce a polypeptide characterized by the amino acid sequence of beta interferon. As I have already explained, once the skilled worker had the DNA sequence of beta interferon in hand, such expression was routine and not an invention. See ¶¶ 55-67.

77. I am informed by Johanne Gauthier of Ogilvy Renault and do verily believe that in Canada, according to the law applicable in this case, an inventor cannot obtain a patent for an invention that was known to another person before he invented it, if that other person had disclosed the invention in such manner that it became available to the public before the inventor filed his first application.

78. In that context, it is my understanding and belief that by mid-April 1980, the amino acid sequence of human beta interferon was known to Drs. Taniguchi and Weissmann and made public through the distribution of the pre-prints of the Taniguchi article without any reserve with respect to its confidentiality. It was also known and made public that the human beta interferon polypeptide is a 166 amino acid mature protein with a 21 amino acid pre- or signal sequence. Thus, after mid-April 1980, I believe that no one could claim to be an inventor "of that sequence" or of the subject matter of any of the conflict claims. The only "novel and inventive" aspect of any of those claims is the DNA sequences that encodes beta interferon. See ¶¶ 55-67, supra.

79. Moreover, the Taniguchi pre-print (Fiers Exhibit 40) was published on June 19, 1980 (Fiers Exhibit 41). That date, I am informed by Mr. Haley, is several months before the September 25, 1980 first priority date of the Goeddel

patent application in this conflict. Dr. Taniguchi had, in fact, published his beta interferon DNA and amino acid sequences even earlier -- May 19, 1980. See Taniguchi et a., *Gene*, 10, pp. 11-15 (1980) (Fiers Exhibit 43).

VI. THE CONFLICT CLAIMS AND MY DATES OF INVENTION

A. The Claims In Conflict Between Biogen, The Japanese Foundation And Genentech

These conflict claims relate to the nucleotide sequence of beta interferon, cloning vectors containing that sequence and hosts transformed with those vectors. As I have explained above (See ¶¶ 7 and 17-20), I believe that conception of each of these claims requires possession of a specific DNA sequence and confirmation that the sequence either corresponds to that known for native beta interferon (Fiers Exhibit 8) or expression of beta interferon activity.

With that sequence in hand, however, I believe that the steps to insert it into a vector and to transform an E.coli host with the vector were obvious and routine. See ¶¶ 55-67. I understand from Johanne Gauthier that as was described in the Christiani case, these obvious steps should not be relevant to determine the date of invention.

80. **Conflict Claim C2**

A nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly

Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn.

(a) Date of Conception

March 25, 1980

On this date, I had a computer print-out depicting the complete DNA sequence that characterized beta interferon. The print-out depicted the DNA encoding pre-beta interferon and the DNA encoding mature beta interferon. On that date, if not before, I believed, a belief that was confirmed by my work, that I would be able to employ my positive clones pHFIF6 and pHFIF7 to produce the DNA sequence depicted in the print-out. And, I believed by that date that the sequence would encode a beta interferon characterized by the amino acid sequence of the conflict claim. See ¶¶ 29-32.

I understand the term "characterized by" to mean in this and the other conflict claims that, although the polypeptide must have as a principal characteristic the recited amino acid sequence, the polypeptide is not necessarily limited to that sequence alone. However, even if the term requires that the polypeptide have only the recited sequence, my conception date would be the same. On March 25, 1980, I had the complete sequence of beta interferon (i.e., the nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence of the conflict claim) and there was no invention required to produce a DNA sequence encoding either a polypeptide having only the recited sequence or having at a minimum that sequence. See ¶¶ 28-32 and 55-67.

(b) Date of First Drawing

March 25, 1980

A DNA sequence is not susceptible to a drawing. However, on March 25, 1980, I had a computer print-out depicting the complete nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence of the conflict claim. See ¶¶ 28-32. The print-out also depicted the DNA sequences that encoded pre- and mature beta interferon.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid and DNA sequences that characterized and encoded beta interferon. On that date, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-out depicted both the DNA sequence that encoded the pre- and mature amino acid sequence of beta interferon. On March 28, 1980, I also disclosed the sequences depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy to Mr. Haley. See ¶¶ 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Between March 25, 1980 and early April 1980, we prepared a composite DNA molecule from pHFIF6 and pHFIF7. It contained a DNA sequence that encoded the recited sequence. The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 note and in Mr. Derynck's report to me that is attached that note (Fiers

Exhibit 23) These steps had followed the protocol that I had determined on March 20, 1980 on the train to Paris that I had disclosed to Dr. Remaut and Mr. Dernyck before March 25, 1980 and to the Biogen Board on March 28, 1980. See ¶¶ 28-32

81. **Conflict Claim C3**

A recombinant vector comprising a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn.

82. **Conflict Claim C5**

A process for preparing a recombinant vector comprising a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn,

which process comprises inserting said nucleotide sequence into a vector.

(a) Date of Conception

March 25, 1980

I note that these claims say nothing about how the recited vector is constructed or the process carried out, except that the DNA sequence is inserted in the vector. This is because all of the steps were well known and routine in the art. The only novel feature of the claimed vector or process is the DNA sequence that encodes the recited polypeptide.

On March 25, 1980 I had a computer print-out of the DNA sequence that encoded a polypeptide characterized by the recited amino acid sequence. On that date, I had already formulated how I would use the DNA sequence to prepare a recombinant vector. See ¶¶ 8-11 and 28-32. And, I knew how to prepare the sequence from pHFIF6 and pHFIF7 and how to insert the composite sequence into a vector. The resulting vector would comprise a DNA encoding the recited amino acid sequence. See ¶¶ 28-32

The term "comprise" is open ended. Therefore, a vector that has, at a minimum, the recited sequence would be within the scope of the conflict claim.

I understand the term "characterized by" to mean in this and the other conflict claims that the polypeptide must have as a principal characteristic the recited amino acid sequence, but the polypeptide is not necessarily limited to that sequence alone. However, even if the term requires that the polypeptide have only the recited sequence, my conception date would be the same.

(b) Date of First Drawing

March 25, 1980

A vector and biological process are not susceptible to a drawing. However, on March 25, 1980, I had the complete nucleotide and amino acid sequence of beta interferon. It was depicted on a computer print-out that my computer technician had generated on that date. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. On that date, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-out depicted both the pre- and mature amino acid sequences of beta interferon. On that date, I also knew how to combine two of my positive clones, pHFIF6 and pHFIF7, to produce the sequence depicted in the print-out. We would use the common PstI restriction site. I had already discussed with Mr. Derynck and Dr. Remaut how to do this before March 25, 1980. See ¶¶ 28-31. And we would use vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy to Mr. Haley. See ¶¶ 28-32. The Board and Mr. Haley knew from my previous discussions with them how I would use the sequence to produce vectors containing the beta interferon nucleotide sequences. See ¶¶ 8-11 and 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Beginning on March 25, 1980, we prepared a composite nucleotide molecule from pHFIF6 and pHFIF7, which encoded a polypeptide characterized by the amino acid sequence of the conflict claim. We inserted that nucleotide sequence into a vector -- pPLa2311. That vector was available and had been used in my laboratory since 1979. The resulting vector 67-12 comprised a DNA sequence encoding the recited amino acid sequence. We made the insertions using standard cloning techniques and hosts. Although all of these steps were completed before April 26, 1980, I considered my date of invention to be March 25, 1980. The additional steps were simply reduction to practice of my invention using standard techniques and protocols that I had discussed with my colleagues and the Biogen Board many times. See ¶¶ 8-11, 28-32, 36-40 and 55-67.

The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 note and in Mr. Derynck's report to me that is attached to my note (Fiers Exhibit 23). See ¶¶ 36-40.

83. **Conflict Claim C4**

E. coli transformed with a recombinant vector comprising a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His

Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn.

84. **Conflict Claim C6**

A process for preparing E. coli containing a recombinant vector comprising a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn,

which process comprises transforming E. coli with said recombinant vector.

(a) Date of Conception

March 25, 1980

I note that these claims say nothing about how the recited E coli host is constructed or the process carried out, except that the host is transformed with a vector that contains the beta interferon DNA sequence. This is because all of the steps were well known and routine. The only novel feature of the claimed host or vector is the DNA sequence that encodes the recited polypeptide.

On March 25, 1980, I had a computer print-out depicting the DNA and nucleotide sequence that encoded the amino acid sequence of human beta interferon (i.e., a polypeptide characterized by the amino acid sequence of the conflict claim). The print-out depicted the DNA and amino acid sequences of pre-beta interferon and

mature beta interferon. On March 25, 1980, I had already formulated how I would use the DNA sequence to construct a vector to transform an E.coli host and discussed it with Mr. Derynck, Dr. Remaut and the Biogen Board. See ¶¶ 8-11 and 28-32. And I knew, on that date, that I would be able to employ the DNA sequence depicted in the print-out to produce a vector containing the sequence (derived from pHFIF6 and pHFIF7) and to use that vector to transform an E.coli host. That host would, thus, comprise (an open-ended term) a nucleotide sequence encoding a polypeptide characterized by the recited amino acid sequence. See ¶¶ 28-32 and 36-40.

I understand the term "characterized by" to mean in this and the other conflict claims that the polypeptide must have as a principal characteristic the recited amino acid sequence, but the polypeptide is not necessarily limited to that sequence alone. However, even if the term requires that the polypeptide have only the recited sequence, my conception date would be the same. On March 25, 1980, I had the complete DNA and amino acid sequences of beta interferon and there was no invention required to produce an E.coli host transformed with a vector comprising a nucleotide sequence encoding either a polypeptide having only the recited sequence or having at a minimum that sequence. See ¶¶ 28-32 and 55-67.

(b) Date of First Drawing

March 25, 1980

An E.coli host or process of transformation is not susceptible to a drawing. However, on March 25, 1980, I had a computer print-out of the complete nucleotide and amino acid sequence of beta interferon that characterized the recited E.coli host. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. On that day, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-out depicted both the pre- and mature amino acid sequences of beta interferon. On that date, I also knew how to combine two of my positive clones, pHFIF6 and pHFIF7, to produce the sequence depicted in the print-out. We would use the common PstI restriction site. I had discussed this with Mr. Derynck and Dr. Remaut just prior to March 25, 1980 when I returned from Paris. And, we would use vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. This was part of the protocol I had disclosed to Mr. Derynck, Dr. Remaut and the Biogen Scientific Board well before March 25, 1980. The only remaining piece to the puzzle to produce the recited E.coli host was the March 25, 1980 DNA sequence. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy of the prior art to Mr. Haley. See ¶¶ 8-11 and 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Between March 25, 1980 and the week of April 21, 1980, we prepared a composite DNA molecule from two of our positive clones pHFIF6 and pHFIF7. We inserted that DNA molecule into an expression vector -- pPL.a2311. That vector was available and had been used in my laboratory since 1979 for the expression of proteins

in E. coli. The resulting 67-12 vector comprised a DNA sequence that encoded a polypeptide characterized by the recited amino acid sequence. We transformed E. coli with that expression vector using standard techniques of molecular biology. Although all of these steps were completed before April 26, 1980, I believe that my date of invention is March 25, 1980. The further steps were simply reduction to practice using standard technology and following protocols I had previously discussed with my colleagues and the Biogen Board.. See ¶¶ 8-11, 29-32 and 55-67.

The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 note and in Mr Derynck's report to me that was attached to my note (Fiers Exhibit 23). See ¶¶ 36-44.

B. The Claims In Conflict Between Biogen And Genentech

These conflict claims all relate the production of beta interferon, using the DNA sequence of beta interferon, intermediates (hosts and expression vectors) used in that production, and compositions containing the produced interferon. As I have discussed above (see ¶¶ 68-79) as of mid-April 1980, the DNA and amino acid sequences of human beta interferon were widely available to the skilled workers in interferon art. Accordingly, anyone whose date of "invention" is after mid-April 1980 cannot claim any invention in the use of that nucleotide sequence to produce a polypeptide characterized by that amino acid sequence. With the nucleotide sequence in hand, such expression was routine and not an invention. See ¶¶ 55-67. The same is true for expression vectors, hosts and processes used in that expression and compositions and uses of the beta interferon produced by them. All of these steps were obvious at the time. Once the DNA sequence was available, to the skilled worker they

could be carried out using standard molecular biology technology. See ¶¶ 55-67. I understand from Johanne Gauthier that as was decided in the Christiani case, these obvious steps should not be relevant to determining the date of invention. See ¶¶ 76-79.

85. **Conflict Claim C1**

An unglycosylated polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn.

(a) Date of Conception

March 25, 1980

The polypeptide as now defined in the conflict claim reads on prior polypeptides used in the art and, thus, is not distinguished from those prior art polypeptides. Unglycosylated beta interferon was known in the art in 1979. See ¶¶ 23(j), 62. Although the complete amino acid sequence of those polypeptides was not known, they were the same beta interferon. They, therefore, had the recited amino acid sequence. Therefore, I do not believe that the polypeptide of conflict claim 1 is patentable.

In any event, and only to satisfy the requirements of the old Canadian Patent Act and Rules, I will discuss my date of "invention" as if this were a valid claim.

I conceived the polypeptide of conflict claim 1 on March 25, 1980. On this date, I had a computer print-out depicting the amino acid sequence that characterized human beta interferon. The print-out depicted both the amino acid sequence of pre-beta interferon and that of mature beta interferon. On that date, I believed, a belief that was confirmed by my work, that I would be able to employ the DNA sequence depicted in the March 25, 1980 print-out to produce an unglycosylated beta interferon that was characterized by the amino acid sequence of the conflict claim. See ¶¶ 28-32 and 55-67. I would simply folllow the protocol that I had already formulated and disclosed to my colleagues and the Biogen Board. See ¶¶ 8-11 and 28-32.

I understand that the term "characterized by" to mean in this and the other conflict claims that, although the polypeptide must have as a principal characteristic the recited amino acid sequence, the polypeptide is not necessarily limited to that sequence alone. However, even if the term requires that the polypeptide have only the recited sequence, my conception date would be the same. On March 25, 1980, I had the complete sequence of beta interferon and there was no invention required to produce either a polypeptide having only the recited sequence or having at a minimum that sequence. See ¶¶ 28-32 and 55-67.

Were the Conflict Examiner to consider it to be an invention to express beta interferon with the DNA sequence in hand, which I believe is not the case, my conception date can be no later than April 26, 1980. On that date I had produced an unglycosylated beta interferon. See ¶¶ 40-45.

(b) Date of First Drawing

March 25, 1980

A polypeptide is not susceptible to a drawing. However, on March 25, 1980, I had a computer print-out of the complete amino acid sequence that characterized beta interferon, as recited in the conflict claim. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. That same day, I also spoke to Mr. Haley about the sequence and save a copy of it to Mr. Volckaert. The print-out depicted both the pre- and mature amino acid sequence of beta interferon. Well before March 25, 1980, I had already discussed many times with Mr. Derynck, Mr. Stanssens and Dr. Remaut the expression constructs that we would use to produce an unglycosylated polypeptide characterized by the amino acid sequence of the conflict claim. We would use vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. As I mentioned earlier, the only remaining piece to the puzzle to enable any person skilled in the art to follow the protocol that I had formulated and disclosed to my colleagues and to the Biogen Scientific Board was the March 25, 1980 DNA sequence (See ¶¶ 8-11 and 28-32). On March 28, 1980, I again disclosed the sequence depicted on the March 25, 1980 computer print-out both to the Biogen Scientific Board and provided a copy of the print-out to Mr. Haley. See ¶¶ 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Between March 25, 1980 and the week of April 21, 1980, we prepared a composite DNA molecule from two of our positive clones pHFIF6 and pHFIF7 (i.e., the two clones from which the March 25, 1980 print-out was derived). We inserted that DNA molecule into an expression vector -- pPLa2311. That vector was available and had been used in my laboratory since 1979 for the expression of proteins in E. coli. The resulting 67-12 vector had the DNA sequence encoding beta interferon located in operative association with the P_L expression control sequence that characterized vector pPLa2311. We transformed E. coli with that expression vector using standard techniques. And, using standard protein isolation techniques and interferon antiviral assays well known at the time, we detected in those transfected cells the production of a biologically active, unglycosylated beta interferon characterized by the recited sequence. Although all of these steps were completed before April 26, 1980, I consider my invention date to be March 25, 1980. The subsequent steps were simply reduction to practice using standard technology and following the protocols that I had previously disclosed to my colleagues and the Biogen Board. See ¶¶ 8-11, 28-32 and 55-67.

The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 note and in Mr. Derynck's report to me that is to that note. See ¶¶ 40-45.

By the week of May 12-16, 1980, we had improved the level of production of a polypeptide characterized by the recited sequence by 20- to 30-fold. In making those improvements, we used the DNA sequence depicted on the March 25,

1980 computer print-out and other available expression vectors. See ¶¶ 46-47. One of the polypeptides was a fusion protein characterized by the recited sequence. The other had a size compatible with a polypeptide having only the recited sequence. See ¶¶ 44-47. All of these steps were obvious at that time to a person skilled in the art using standard molecular biology technology. See ¶¶ 55-67. Thus, I understand from Johanne Gauthier that as was decided in the Christiani case, they should not be relevant to determining my date of invention. See ¶¶ 76-79.

86. **Conflict Claim C7**

A recombinant vector comprising, in operative association, an expression control sequence and a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn

87. **Conflict Claim C9**

A process for preparing a recombinant vector wherein said vector comprises, in operative association, an expression control sequence and a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His

Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn,

which process comprises inserting said nucleotide sequence into a vector which comprises said expression control sequence.

(a) Date of Conception

March 25, 1980

I note that these claims say nothing about how the recited vector is constructed or the process carried out, except that the DNA sequence is inserted into the vector in operative association with an expression control sequence. This is because all of the steps were well known. The only novel feature is the DNA that encodes the recited polypeptide.

On March 25, 1980 I had a computer print-out of the DNA sequence that encoded a polypeptide characterized by the recited amino acid sequence. On that date, I had already formulated how I would use the sequence and had disclosed that protocol to Dr. Remaut, Mr. Derynck and the Biogen Board. See ¶¶ 8-11 and 28-32. And, I knew how to prepare the sequence from pHFIF6 and pHFIF7 and how to insert the composite sequence into an expression vector and locate the DNA sequence in operative association with an expression control sequence. The resulting vector would comprise a DNA encoding the recited amino acid sequence. See ¶¶ 28-32 and 36-46.

The term "comprise" is open ended. Therefore, a vector that has, at a minimum, the recited sequence would be within the scope of the conflict claim.

(b) Date of First Drawing

March 25, 1980

A vector and biological process are not susceptible to a drawing. However, on March 25, 1980, I had the complete nucleotide and amino acid sequence of beta interferon. It was depicted on a computer print-out that my computer technician had generated on that date. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. On that date, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-out depicted both the pre- and mature amino acid sequences of beta interferon. On that date, I also knew how to combine two of my positive clones, pHFIF6 and pHFIF7, to produce the sequence depicted in the print-out. We would use the common PstI restriction site. I had discussed that protocol with Mr. Derynck and Dr. Remaut before March 25, 1980 when I returned from Paris. See ¶¶ 28-32. And, we would use expression vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. The only remaining piece to the puzzle for producing expression vectors was the March 25, 1980 DNA sequence. I had already discussed with Mr. Derynck and Dr. Remaut how to use this piece of the puzzle well before the March 25, 1980 date to make an expression vector containing it. It would be inserted into the vectors and located in them in operative association with an expression control sequence, just as we had already done for various other DNA

sequences that encoded proteins. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy to Mr. Haley. See ¶¶ 28-32. The Board and Mr. Haley knew from my previous presentations how I would use the sequence to produce an expression vector able to produce beta interferon in an E.coli host. See ¶¶ 8-11 and 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Beginning on March 25, 1980, we prepared a composite nucleotide molecule from pHFIF6 and pHFIF7 which encoded a polypeptide characterized by the amino acid sequence of the conflict claim. We inserted that nucleotide sequence into an expression vector -- pPLa2311 -- where the sequence was in operative association with an expression control sequence. That vector was available and had been used in my laboratory since 1979. The resulting vector 67-12 comprised a DNA sequence encoding the recited amino acid sequence. We made the insertions using standard cloning techniques and hosts. Although, all of these steps were completed before April 26, 1980, I consider that I am entitled to an invention date of March 25, 1980, as these further steps were simply a reduction to practice of the plan I had made long before and discussed with my colleagues and the Biogen Board. It required only standard technology teachings and routine skill. See ¶¶ 28-45 and 55-67.

The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 note and in Mr. Derynck's report to me that is attached to my note (Fiers Exhibit 23). See ¶¶ 40-45.

88. **Conflict Claim C8**

E. coli transformed with a recombinant vector wherein said vector comprises, in operative association, an expression control sequence and a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn.

89. **Conflict Claim C10**

A process for preparing E. coli containing a recombinant vector wherein said vector comprises, in operative association, an expression control sequence and a nucleotide sequence which encodes a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn,

which process comprises transforming E. coli with said recombinant vector.

(a) Date of Conception

March 25, 1980

I note that these claims say nothing about how the recited E coli is produced or the process carried out, except that the host is transformed with a vector having the DNA sequence encoding beta interferon in operative association with an expression control sequence. This is because all of the steps were well known. The only novel feature of the host and process is the DNA that encodes the recited polypeptide.

On March 25, 1980 I had a computer print-out of the DNA sequence that encoded a polypeptide characterized by the recited amino acid sequence. On that date, I had already formulated a plan to prepare an E.coli host able to express and produce beta interferon and discussed that plan with my colleagues and the Biogen Board. See ¶¶ 8-11 and 28-32. I knew how to prepare the sequence from pHFIF6 and pHFIF7 and how to insert the composite sequence into an expression vector. The resulting vector would comprise a DNA encoding the recited amino acid sequence in operative association with an expression control sequence. See ¶¶ 28-32 and 36-45. The term "comprise" is open ended. Therefore, a vector that has, at a minimum, the recited sequence would be within the scope of the conflict claim.

(b) Date of First Drawing

March 25, 1980

An E.coli host and biological process are not susceptible to a drawing. However, on March 25, 1980, I had the complete nucleotide and amino acid sequence of beta interferon. It was depicted on a computer print-out that my computer technician generated on that date. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. On that date, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-out depicted both the pre- and mature amino acid sequences of beta interferon. On that date, I also knew how to combine two of my positive clones, pHFIF6 and pHFIF7, to produce the sequence depicted in the print-out. We would use the common PstI restriction site. I had discussed that protocol with Mr. Derynck and Dr. Remaut before March 25, 1980 when I returned from Paris. See ¶¶ 28-32. And we would use vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. This was part of the protocol that I had disclosed to Mr. Derynck, Dr. Remaut and the Biogen Scientific Board before March 25, 1980. The only remaining piece to the puzzle to produce the claimed host was the March 25, 1980 DNA sequence. With that DNA sequence, we would insert it into an expression vector in operative association with an expression control sequence and transform an E.coli host cell with the vector. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy to Mr. Haley. See ¶¶ 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Beginning on March 25, 1980, we prepared a composite nucleotide molecule from pHFIF6 and pHFIF7. We inserted that nucleotide sequence into an

expression vector -- pPLa2311. That vector was available and had been used in my laboratory since 1979. The resulting vector 67-12 comprised a DNA sequence encoding the recited amino acid sequence in operative association with an expression control sequence. We made the insertions using standard cloning techniques and hosts. The recombinant vector was then used to transform an E.coli host. The host was characterized by a vector that comprises a nucleotide sequence that encodes a polypeptide characterized by the recited sequence. Although, all of these steps were completed before April 26, 1980, I considered my invention complete on March 25, 1980. The further steps were simply reduction to practice using standard methodology of the plan I made long before and discussed with my colleagues and the Biogen Board. See ¶¶ 8-11, 28-32 and 55-67.

The results of these April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 note and in Mr. Derynck's report to me that is attached to my note (Fiers Exhibit 23). See ¶¶ 40-45.

90. **Conflict Claim C11**

A process for preparing a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn,

which process comprises

(a) transforming E. coli with a recombinant vector wherein said vector comprises, in operative association, an expression control sequence and a nucleotide sequence which encodes said polypeptide, and

(b) culturing the transformed E. coli to produce said polypeptide.

(a) Date of Conception

March 25, 1980

I note that this claim says nothing about how the process is carried out, except that an E.coli host is transformed with a vector having a DNA sequence for beta interferon in operative association with an expression control sequence. This is because all of the steps were well known. The only novel feature of the process is the DNA sequence that encodes the recited polypeptide.

On March 25, 1980, I had a computer print-out depicting the DNA and amino acid sequences that characterized human beta interferon. The print-out depicted both the amino acid sequence of pre-beta interferon and of mature beta interferon. By that date, I had already formulated a plan to produce beta interferon in E coli using my cloned DNA in an expression vector and disclosed that plan to my colleagues and the Biogen Board. See ¶¶ 8-11 and 28-32. And, I believed, a belief confirmed by my work, that I would be able to employ the DNA sequence depicted in the print-out and constructed using pHFIF6 and pHFIF7 to produce an unglycosylated beta interferon in E. coli that was characterized by the amino acid sequence of the conflict claim. See ¶¶ 28-32 and 36-45. None of these steps would require invention. See ¶¶ 55-67. They were the routine application of standard molecular biology techniques to my DNA sequences an followed my original protocol. See ¶¶ 8-11 and 28-32. The resulting vector and host would comprise my beta interferon DNA sequences.

I understand the term "characterized by" to mean in this and the other conflict claims that, although the polypeptide must as a principal characteristic have the recited amino acid sequence, the polypeptide is not necessarily limited to that sequence alone. However, if the term requires that the polypeptide have only the recited sequence, my conception date would be the same. See ¶¶ 8-11, 28-32 and 40-45.

Were the Conflict Examiner to consider it to be an invention to produce beta interferon with the DNA sequence in hand, which I believe is not the case, my conception date is no later than April 26, 1980. On that date I had produced an unglycosylated beta interferon by transforming E.coli with a vector comprising, in operative association, an expression control sequence and a nucleotide sequence which encodes a beta interferon polypeptide and culturing the host to produce the interferon. See ¶¶ 28-45.

(b) Date of First Drawing

March 25, 1980

A process is not susceptible to a drawing. However, on March 25, 1980, I had the complete DNA and amino acid sequences of beta interferon. They were part of two overlapping sequences (pHFIF6 and pHFIF7) that I recognized could be combined to yield the complete sequence. I printed out the composite sequence on March 25, 1980. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. On that same day, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-out depicted both the pre- and mature amino acid sequences of beta interferon. Well before March 25, 1980, I had already discussed many times with Mr. Derynck, Mr. Stanssens and Dr. Remaut the expression constructs that we would use to produce an unglycosylated polypeptide characterized by the amino acid sequence of the conflict claim. See ¶¶ 8-11 and 28-32. We would use vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. The only remaining piece to the puzzle to produce recombinant beta interferon was the March 25, 1980 DNA sequence. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy to Mr. Haley. See ¶¶ 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Between March 25, 1980 and the week of April 21, 1980, we prepared a composite DNA molecule from two of our positive clones pHFIF6 and pHFIF7. We inserted that DNA molecule into an expression vector -- pPLa2311. That vector was available and had been used in my laboratory since 1979 for the expression of proteins in E. coli. The resulting 67-12 vector had the DNA sequence encoding beta interferon located in operative association with the P_L expression control sequence that

characterized vector pPLa2311. We transformed E. coli with that expression vector using standard techniques. And, we detected the production of a biologically active, unglycosylated beta interferon characterized by the recited sequence in those transfected cells using standard protein isolation techniques and interferon antiviral assays. Although all of these steps were completed before April 26, 1980, I consider my date of invention to be March 25,1980. The further steps were simply reduction to practice using standard and well known technology and following my long planned protocol that I had discussed with my colleagues and the Biogen Board. See ¶¶ 8-11, 28-32, 40-45 and 55-67.

The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, my April 26, 1980 note and in Mr. Derynck's report to me that is attached to my note (Fiers Exhibit 23). See ¶¶ 40-45.

By the week of May 12-16, 1980, we had improved the level of production of a polypeptide characterized by the recited sequence by 20- to 30-fold. In making those improvements, we used the DNA sequence depicted on the March 25, 1980 computer print-out and available expression vectors. One of the polypeptides was a fusion portion characterized by the recited sequence. The other had a size compatible with a polypeptide having only the recited sequence. See ¶¶ 46-47.

91. **Conflict Claim C17**

A process for producing a polypeptide which contains the amino acid sequence of human fibroblast interferon, which process comprises

(a) obtaining mRNA from human fibroblasts,
(b) preparing double-stranded cDNA from said mRNA,
(c) inserting said cDNA into a plasmid,
(d) transforming E. coli with said plasmid,

(e) detecting and isolating a transformant which expresses said interferon, and

(f) culturing the isolated transformant of step (e) to produce said interferon.

(a) Date of Conception

March 25, 1980

Each of the steps recited in this claim were part of my early 1978 protocol for cloning and expressing beta interferon. They are merely standard technology. The only novel part of the claim is the DNA sequence of beta interferon. It is that sequence that allows a host transformed within it to produce beta interferon.

I had that DNA sequence on March 25, 1980.

On that date, I had a computer print-out depicting the DNA and amino acid sequences that characterized human beta interferon. The print-out depicted both the amino acid sequence of pre-beta interferon and that of mature beta interferon. On that date, I believed, a belief that was confirmed by my work, that I would be able to employ the DNA sequence depicted in the print-out to produce a polypeptide which contains the amino acid sequence of human fibroblast interferon in E. coli using standard technology and following my protocol that I had previously disclosed to my colleagues and the Biogen Board. See ¶¶ 8-11 and 28-32.

I understand that the term "contains" is open-ended. It means that, although the polypeptide must at a minimum include amino acid sequences of fibroblast interferon, the polypeptide is not limited to that sequence alone. However, even were the term to require that the polypeptide have only sequence of fibroblast interferon, my conception date would be the same. On March 25, 1980, I had the complete sequence of beta interferon and there was no invention required to produce

either a polypeptide having only the recited sequence or having at a minimum that sequence. See ¶¶ 28-32 and 55-67.

Were the Conflict Examiner to consider it to be an invention to express beta interferon with the DNA sequence in hand, which I believe is not the case because the methods to produce proteins in E.coli were well known before March 25, 1980, my conception date is no later than April 26, 1980. On that date, I had produced an unglycosylated beta interferon. See ¶¶ 40-45.

(b) Date of First Drawing

A process is not susceptible to a drawing. However, on March 25, 1980, I had a computer print-out of the complete DNA and amino acid sequences that characterized human fibroblast interferon. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. On that date, the members of my laboratory, including Mr. Derynck and Dr. Remaut, as well as Mr. Haley, were well aware of the RNA/cDNA- based process by which I had isolated the DNA sequence. The print-out depicted both the pre- and mature amino acid sequences of beta interferon. Well before March 25, 1980, I had already discussed many times with Mr. Derynck, Mr. Stanssens and Dr. Remaut the expression constructs that we would use to produce an unglycosylated polypeptide characterized by the amino acid sequence of the conflict claim. See ¶¶ 8-11 and 28-32. We would use vectors

available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. The only remaining piece to the puzzle to produce beta interferon was the March 25, 1980 DNA sequence. With that sequence it was straight forward and simple to produce beta interferon in E.coli. See ¶¶ 55-67. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out with the Biogen Scientific Board and provided a copy to Mr Haley. See ¶¶ 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Between March 25, 1980 and the week of April 21, 1980, we prepared a composite DNA molecule from two of our positive clones pHFIF6 and pHFIF7. The two positive clones were derived from the screening of cDNA libraries prepared from the mRNA of human fibroblasts. We inserted that composite DNA molecule into an expression vector -- pPLa2311. That vector was available and had been used in my laboratory since 1979 for the expression of proteins in E. coli. The resulting 67-12 vector had the DNA sequence encoding beta interferon located in operative association with the P_L expression control sequence that characterized vector pPLa2311. We transformed E. coli with that expression vector using standard techniques. And, using standard E.coli culturing techniques, protein isolation techniques and interferon antiviral assays, we detected in those transfected cells the production of a biologically active, unglycosylated beta interferon characterized by the recited sequence. See ¶¶ 36-45. All of these steps were completed before April 26, 1980, I believe my date of invention is March 25, 1980. The further steps were simply reduction to practice using the standard techniques and following the protocol that I

had disclosed before March 25, 1980 to my colleagues and the Biogen Board. See ¶¶ 40-45 and 55-67.

The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 notes and in Mr. Derynck's report to me that is attached to my note (Fiers Exhibit 23). See ¶¶ 40-45.

By the week of May 12-16, 1980, we had improved the level of production of a polypeptide characterized by the recited sequence by 20- to 30-fold. In making those improvements, we used the DNA sequence depicted on the March 25, 1980 computer print-out and available expression vectors. See ¶¶ 46-47.

92. **Conflict Claim C18**

A composition for treating human tumors and viruses comprising a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn

in admixture with a pharmaceutically acceptable carrier or diluent.

93. **Conflict Claim C19**

Use of a polypeptide characterized by the amino acid sequence

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn

for the preparation of a composition for treating human tumors and viruses.

(a) Date of Conception

March 25, 1980

These conflict claims are not novel over available compositions of native beta interferon. These compositions were well known before 1979 and had long been used by that date to treat human tumors and viruses. See, e.g., my Canadian patent application, pp. 4-7 and the references cited therein. Thus, there can be no invention in these claims.

If the conflict claims for some reason are inventive, I conceived them on March 25, 1980

On this date, I had a computer print-out depicting the amino acid sequence that characterized human beta interferon. The print-out depicted both the amino acid sequence of pre-beta interferon and that of mature beta interferon. On that date, I believed, a belief that my later work would confirm, that I would be able to employ the DNA sequence depicted in the print-out to produce an unglycosylated beta interferon in E. coli that was characterized by the amino acid sequence of the conflict claim. See ¶¶ 8-11, 28-32, 40-45 and 55-67 I had discussed the protocol that I would use with Dr. Remaut, Mr. Derynck and the Biogen Board many times before March 25, 1980. See ¶¶ 8-11 and 28-32.

I understand the term "characterized by" to mean in this and the other conflict claims that, although the polypeptide must have as a principal characteristic the recited amino acid sequence, the polypeptide is not necessarily limited to that sequence alone. However, even if the term requires that the polypeptide have only the recited sequence, my conception date would be the same. On March 25, 1980, I had the complete sequence of beta interferon and there was no invention required to produce either a polypeptide having only the recited sequence or having at a minimum that sequence or to produce a composition characterized by it for use in the treatment of tumors or viruses. See ¶¶ 28-32 and 55-67.

Were the Conflict Examiner to consider it to be an invention to express beta interferon with the DNA sequence in hand, which I believe is not the case, my conception date is no later than April 26, 1980. On that date I had produced an unglycosylated beta interferon. See ¶¶ 28-44.

(b) Date of First Drawing

March 25, 1980

A composition and use are not susceptible to a drawing. However, on March 25, 1980, I had a computer print-out of the complete amino acid sequence that characterized beta interferon, as recited in the conflict claim. See ¶¶ 28-32.

(c) Date and Mode of First Written or Oral Disclosure

March 25-28, 1980

On March 25, 1980, I discussed with members of my laboratory, including Dr. Remaut and Mr. Derynck, my March 25, 1980 computer print-out of the amino acid sequence that characterized beta interferon. On that same day, I also spoke to Mr. Haley about the sequence and gave a copy of it to Mr. Volckaert. The print-

out depicted both the pre- and mature amino acid sequences of beta interferon. Well before March 25, 1980, I had already discussed many times with Mr. Derynck, Mr. Stanssens and Dr. Remaut the expression constructs that we would use to produce an unglycosylated polypeptide characterized by the amino acid sequence of the conflict claim. See ¶¶ 8-11 and 28-32. We would use vectors available in our laboratory, well-known E. coli hosts, and the standard techniques of molecular biology. The produced polypeptide would then be used to prepare compositions for use in treating human tumors and viruses just as native beta interferon had been used to prepare those compositions for many years. The only remaining piece to the puzzle to produce beta interferon was the March 25, 1980 DNA sequence. With that sequence it was straight forward to produce recombinant beta interferon and prepare compositions using it. See ¶¶ 40-45 and 55-67. On March 28, 1980, I also disclosed the sequence depicted on the March 25, 1980 computer print-out to the Biogen Scientific Board and provided a copy to Mr. Haley. See ¶¶ 28-32.

(d) Dates and Nature of Successive Steps to Develop and Perfect

Between March 25, 1980 and the week of April 21, 1980, we prepared a composite DNA molecule from two of our positive clones pHFIF6 and pHFIF7. We inserted that DNA molecule into an expression vector -- pPLa2311. That vector was available and had been used in my laboratory since 1979 for the expression of proteins in E. coli. The resulting 67-12 vector had the DNA sequence encoding beta interferon located in operative association with the P_L expression control sequence that characterized vector pPLa2311. We transformed E. coli with that expression vector using standard techniques. And, we detected the production of a biologically active,

unglycosylated beta interferon characterized by the recited sequence in those transfected cells using standard protein isolation techniques and interferon antiviral assays. See ¶¶ 40-45. Although, all of these steps were completed before April 26, 1980, I believe that my invention was complete non March 25, 1980. The further steps were simply reduction to practice using standard techniques and following protocol I had disclosed with my colleagues and the Bidgen Board before March 25, 1980. See ¶¶ 40-45 and 55-67.

The results of those April 1980 activities are described in the laboratory notebooks of Dr. Remaut and Mr. Derynck, in my April 26, 1980 note and in Mr. Derynck's report to me that is attached to my note (Fiers Exhibit 23). See ¶¶ 40-45.

By the week of May 12-16, 1980, we had improved the level of production of a polypeptide characterized by the recited sequence by 20- to 30-fold. In making those improvements, we used the DNA sequence depicted on the March 25, 1980 computer print-out and available expression vectors. One of the polypeptides was a fusion portion characterized by the recited sequence. The other had a size compatible with a polypeptide having only the recited sequence. See ¶¶ 46-47. These polypeptides had shown antiviral activity in our standard assays. They were, therefore, useful to prepare compositions for use in therapy against human tumors and viruses

94. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are verily believed to be true.

19/11/01
Date

Walter C. Fiers

Seen by us, Christof Gheeraert, notary public at Gent, Drongen, for legalisation of the Signature of

Done at Gent, the 19.11.01